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The EASL–*Lancet* Liver Commission: protecting the next generation of Europeans against liver disease complications and premature mortality

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Executive summary

Liver diseases have become a major health threat across Europe, and the face of European hepatology is changing due to the cure of viral hepatitis C and the control of chronic viral hepatitis B, the increasingly widespread unhealthy use of alcohol, the epidemic of obesity, and undiagnosed or untreated liver disease in migrant populations. Consequently, Europe is facing a looming syndemic, in which socioeconomic and health inequities combine to adversely affect liver disease prevalence, outcomes, and opportunities to receive care. In addition, the COVID-19 pandemic has magnified pre-existing challenges to uniform implementation of policies and equity of access to care in Europe, arising from national borders and the cultural and historical heterogeneity of European societies. In following up on work from the *Lancet* Commission on liver disease in the UK and epidemiological studies led by the European Association for the Study of the Liver (EASL), our multidisciplinary Commission, comprising a wide range of public health, medical, and nursing specialty groups, along with patient representatives, set out to provide a snapshot of the European landscape on liver diseases and to propose a framework for the principal actions required to improve liver health in Europe. We believe that a joint European process of thinking, and construction of uniform policies and action, implementation, and evaluation can serve as a powerful mechanism to improve liver care in Europe and set the way for similar changes globally.

On the basis of these data, we present ten actionable recommendations, half of which are oriented towards health-care providers and half of which focus primarily on health policy. A fundamental shift must occur, in which health promotion, prevention, proactive case-finding, early identification of progressive liver fibrosis, and early treatment of liver diseases replace the current emphasis on the management of end-stage liver disease complications. A considerable focus should be put on underserved and marginalised communities, including early diagnosis and management in children, and we provide proposals on how to better target disadvantaged communities through health promotion, prevention, and care using multilevel interventions acting on current barriers.

Underlying this transformative shift is the need to enhance awareness of the preventable and treatable nature of many liver diseases. Therapeutic nihilism, which is prevalent in current clinical practice across a range of medical specialities as well as in many patients themselves, has to end. We wish to challenge medical specialty protectionism and invite a broad range of stakeholders, including primary care physicians, nurses, patients, peers, and members of relevant communities, along with medical specialists trained in obesity, diabetes, liver disease, oncology, cardiovascular disease, public health, addictions, infectious diseases, and more, to engage in integrated person-centred liver patient care across classical medical specialty boundaries. This shift includes a revision in how we converse about liver disease and speak with our patients, and a reappraisal of disease-related medical nomenclature conducted to increase awareness and reduce the social stigmatisation associated with liver disease.

Reimbursement mechanisms and insurance systems must be harmonised to account for patient-centric, multimorbidity models of care across a range of medical specialties, and the World Health Assembly resolution to improve the transparency and fairness of market prices for medicines throughout Europe should be reinforced. Finally, we outline how Europe can move forward with implementation of effective policy action on taxation, food reformulation, and product labelling, advertising, and availability, similar to that implemented for tobacco, to reduce consumption of alcohol, ultra-processed foods, and foods with added sugar, especially among young people. We should utilise the window of opportunity created by the COVID-19 pandemic to overcome fragmentation and the variability of health prevention policies and research across Europe. We argue that the liver is a window to the 21st-century health of the European population. Through our proposed syndemic approach to liver disease and social and health inequities in Europe, the liver will serve as a sentinel for improving the overall health of European populations.

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Key messages

- Liver disease is now the second leading cause of years of working life lost in Europe, after only ischaemic heart disease
- The clinical focus in patients with liver disease is oriented towards cirrhosis and its complications, whereas early and reversible disease stages are frequently disregarded and overlooked
- The dissociation between primary and secondary care and the considerable heterogeneity across clinical pathways and inconsistent models of care cause delays in diagnosis of both rare and common liver diseases
- Stigma has a major impact on liver diseases in Europe, leading to discrimination, reduction in health-care seeking behaviour, and reduced allocation of resources, which all result in poor clinical outcomes
- Europe has the highest level of alcohol consumption in the world, which, together with ultra-processed food consumption and high prevalence of obesity, are the major drivers of liver-related morbidity and mortality
- A scarcity of consistent and efficient screening and vaccination programmes for viral hepatitis combined with the high costs of drugs due to variable European reimbursement systems result in reduced access to treatment and delays in elimination programmes
- COVID-19, alongside imposing delays in diagnostic pathways of liver diseases, has brought overlapping metabolic risk factors and social inequities into the spotlight as crucial barriers to liver health for the next generation of Europeans
- Liver diseases are generally avoidable or treatable if measures for prevention and early detection are properly implemented; achieving this would reduce premature morbidity and mortality, saving the lives of almost 300 000 people across Europe each year

A new era of European hepatology

Liver disease is frequently silent, and ongoing liver injury might result in few overt symptoms and signs until end-stage liver disease has developed. Silent also is the voice of those with liver disease; liver diseases frequently affect the most vulnerable and unrepresented sectors of society. The decisive silence is the absence of political will for implementing population-level policies to overcome the social and environmental factors and health inequities that synergistically drive some of the key causes of liver disease: unhealthy alcohol consumption and obesity. Far beyond the liver, alcohol and ultra-processed foods represent key health challenges in the 21st century, and it is increasingly clear that liver disease acts as a cipher for health and a sentinel for our public health capacity.

Three important factors show that it is time to reconsider liver diseases and their management.[1,2] The advent of direct-acting antiviral drugs marked the end of a 30-year translational journey from the discovery of the hepatitis C virus (HCV) as the cause for non-A, non-B hepatitis, to a definitive cure.[3] Apart from vaccines, there are only a few examples of such transformative drug developments in medicine, and the importance of discovering the virus was recognised by the award of the 2020 Nobel Prize in Physiology and Medicine.[4] Second, the major adverse impacts of type 2 diabetes and obesity on outcomes during the COVID-19 pandemic have revealed the deleterious effect of poor underlying health and galvanised opinions on the importance of policy interventions to deal with rising population-levels of obesity.[5,6] The pandemic has also highlighted the need for rapid, at-scale, point-of-care testing and appropriate vaccination programmes for infectious agents, emphasising in particular the existing public health deficits for hepatitis B virus (HBV) and HCV infection.[7] Finally, although improvements in medicine have been driven by specialisation, there is an increasing realisation of the importance of multiple linked morbidities and hence the need for multidisciplinary teams of primary care physicians, nurses, allied health professionals, and other specialists to deliver high-quality care efficiently.[8] Non-alcohol fatty liver disease (NAFLD) exemplifies the need for conjoined working between hepatologists, diabetologists, dietitians, cardiologists, and general practitioners (GPs), as well as public health action on prevention.[9,10]

These challenges resonate through European hepatology given the ageing population and changes in demography caused by immigration from areas with a higher prevalence of HBV, HCV, and hepatitis D virus (HDV, also known as hepatitis delta virus). An increase in the prevalence of obesity in younger people and liver disease emanating from low social status areas adds to the burden of liver disease. In addition, Europe has the highest level of alcohol consumption in the world, and more than 50% of end-stage liver disease is due to unhealthy levels of alcohol consumption.[11] The *Lancet* Commission on liver disease in the UK has provided strong examples of the challenges in implementing effective regulations and policy measures against obesity and alcohol-related liver disease.[12,13] The European Association for the Study of the Liver (EASL) Hepahealth project has also shown substantial geographical variability within Europe: some areas have low or decreasing liver-related mortality, whereas it remains high and is increasing in other areas.[14] Although there might be policy or legislative solutions to prevent many liver diseases, these are often met with policy inertia, with governments reluctant to introduce them, largely driven by the actions of vested interest groups[11] and an absence of public demand for action.[15]

In this Commission report, we will detail the challenges and propose solutions. The realisation that many liver diseases are preventable provides an important opportunity, although this will require concerted efforts to make the case for change both to the public and

to governments. For medical professionals, early identification of progressive forms of liver disease, at scale, will be clinically important, as will new models of delivering care that incorporate the power of digital health care and multidisciplinary skills. We reinforce the need to work with medical specialties beyond the liver, to increase awareness and recognition in other disciplines. Liver disease is positioned to take on the role as a canary in the coalmine for the health of the next generation of Europeans.

Risk factors in Europe and the burden of liver disease

Chronic liver disease has a substantial impact on young and middle-aged individuals in their prime working years, with the peak age of death occurring in the late 40s and early 50s. This outcome contrasts with mortality from smoking-related and obesity-related illnesses, such as lung cancer or type 2 diabetes, for which deaths typically occur in the 60s and 70s (figure 1). Consequently, WHO data show that liver disease is now second only to ischaemic heart disease as the leading cause of years of working life lost in Europe (figure 2; appendix p 30). In fact, on average, two-thirds of all potential years of life lost due to mortality from liver diseases are years of working life.[14]

Chronic liver disease led to 287 000 deaths in Europe in 2019 (95% CI 268 000–306 000), of which 63 500 (58 916–67 530) were due to primary liver cancer. Liver-related deaths accounted for 3% of all deaths in Europe in 2019, which is an increase from the 204 000 deaths in 1990 (2·3% of all deaths). These changes equate to a 25% increase in deaths due to chronic liver disease and a 70% increase in deaths due to primary liver cancer.[16] The contrasting changes over time in liver-related mortality between countries (figure 3) can be captured by categorising them into five groups: low, decreasing, increasing, high, and an intermediate category with no clear trend (appendix p 38). Understanding the underlying reasons for this wide variability holds important lessons for Europe and the world beyond.

In establishing a data-driven basis for recommendations in this Commission, information on the causes of liver disease was collected from several sources, each with some inherent strengths and weaknesses. Death certification data collated by WHO are known to underreport liver deaths as, in some countries, they are derived from interviews with family members.[17] In Europe, alcohol consumption is by far the leading cause of liver-related mortality but the cause of liver disease is frequently not recorded on death certificates (appendix p 31), and similar issues arise with the coding of hospital admissions.[18] Indeed, in some European countries, 80% of deaths related to liver disease do not have a recorded cause.[19] These problems of reported liver-related deaths can also be illustrated by comparing data from

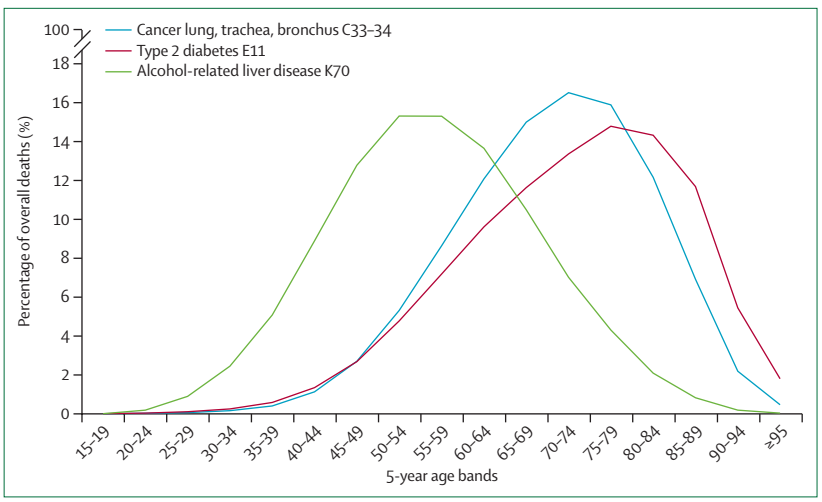

Figure 1: **Distribution of age of death in diseases typically related to smoking, obesity, and alcohol**
Percentage of overall deaths within 5-year age bands from specified diseases related to smoking, obesity, and alcohol intake (with the relevant ICD-10 codes). Patients die from alcohol-related liver disease in their 30s, 40s, and 50s, whereas deaths from smoking-related and obesity-related illness typically occur at a much later age (appendix p 11). Analysis by Nick Sheron. ICD=International Classification of Diseases.

England and Wales in a single year (appendix p 39). In the modelled Global Burden of Disease (GBD) estimates, the proportions of liver-related deaths attributed to alcohol in England and Wales were similar to those recorded directly on death certificates, whereas deaths due to NAFLD were 42% higher and deaths due to viral hepatitis were 7 times higher (appendix p 39). An alternative approach taken by the GBD study is to use the cause of death on death records only to classify deaths as due to cirrhosis or liver cancer, and to model what proportion can be attributed to different causes on the basis of the proportions observed in representative cirrhosis and liver cancer case series (appendix p 31). There is, however, consistency between the WHO and GBD data (appendix p 31) and, since GBD modelling probably represents the best resource, data from the 2019 report were analysed for this Commission.

The scope of this work goes beyond the EU and spans the WHO definition of Europe. Due to limitations in the available data, our reporting and descriptions are regional for several topics—eg, comprising the EU; the EU and the European Economic Area (EEA), including Switzerland, the UK, and Russia in some instances; as well as single countries or areas for some examples with data from case studies. The problem of maintaining a consistent definition of Europe for all aspects of this report is related to some of the problems the Commission has been mandated to query.

The European landscape of risk factors and liver disease

The progression from having a healthy liver to progressive fibrosis, cirrhosis, liver failure and related complications, and, in some cases, liver cancer occurs in response to multiple risk factors and disease mechanisms (figure 4). A diagnostic emphasis on the identification of

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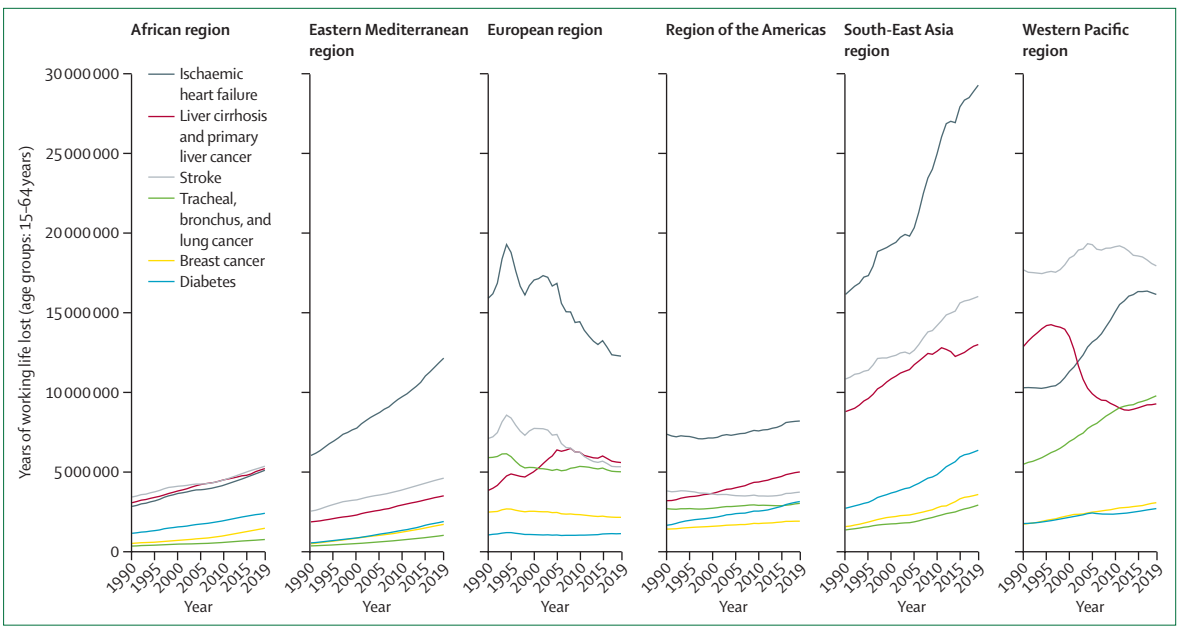

Figure 2: **Potential years of working life lost and leading causes by WHO region**
Years of life lost to adults in working age groups (aged 15–64 years) due to six leading causes of death (1990–2019), as estimated by the Global Burden of Disease study 2019 (appendix pp 11–12). Analysis by Nick Sheron.

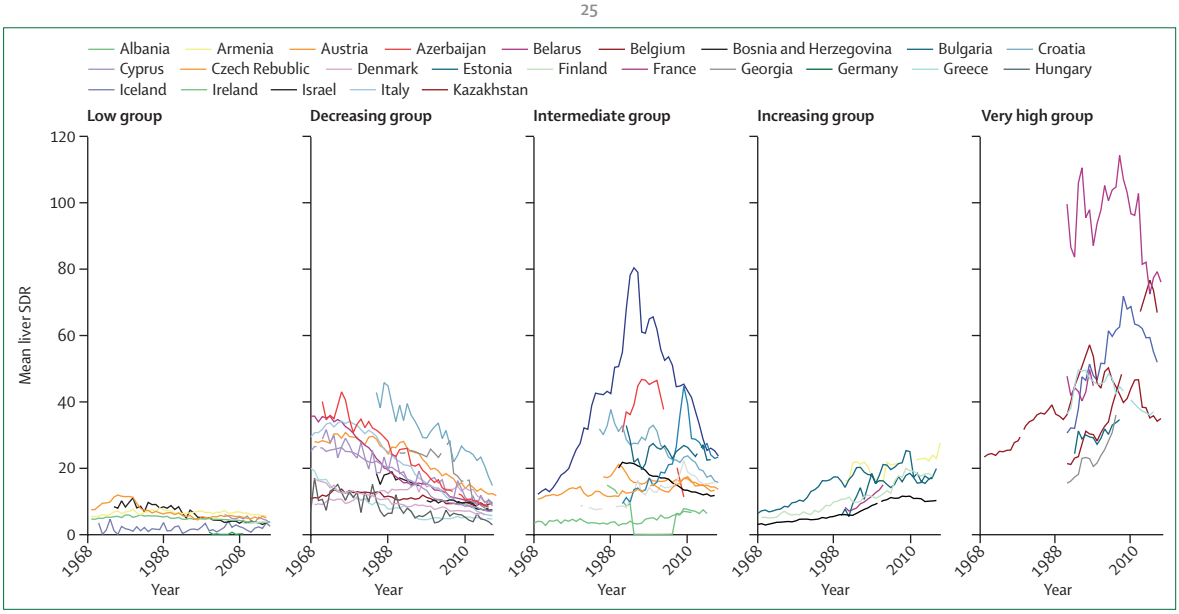

Figure 3: **Liver-related mortality trajectories in countries of the WHO European region**
Different countries within the WHO European region have different trajectories of liver-related mortality during 1968–2016, as shown by standardised death rates (SDR; appendix p 12). Analysis by Nick Sheron.

those at risk of progression by these final, common pathways of end-stage liver disease has important implications for the simplification of case-finding and patient referral, which should focus on the detection of progressive disease with a high risk of complications. At present, liver disease investigation is dominated by minor blood abnormalities, yet most individuals with such abnormalities will never develop serious disease. However, people with undiagnosed cirrhosis, the majority of whom have normal blood tests, remain undetected; we need to find these people earlier. It often takes a long time to develop liver disease complications, sometimes decades, and this inherent resilience of the liver also means that multiple risk factors acting in synergy should always be considered in progressive liver disease.

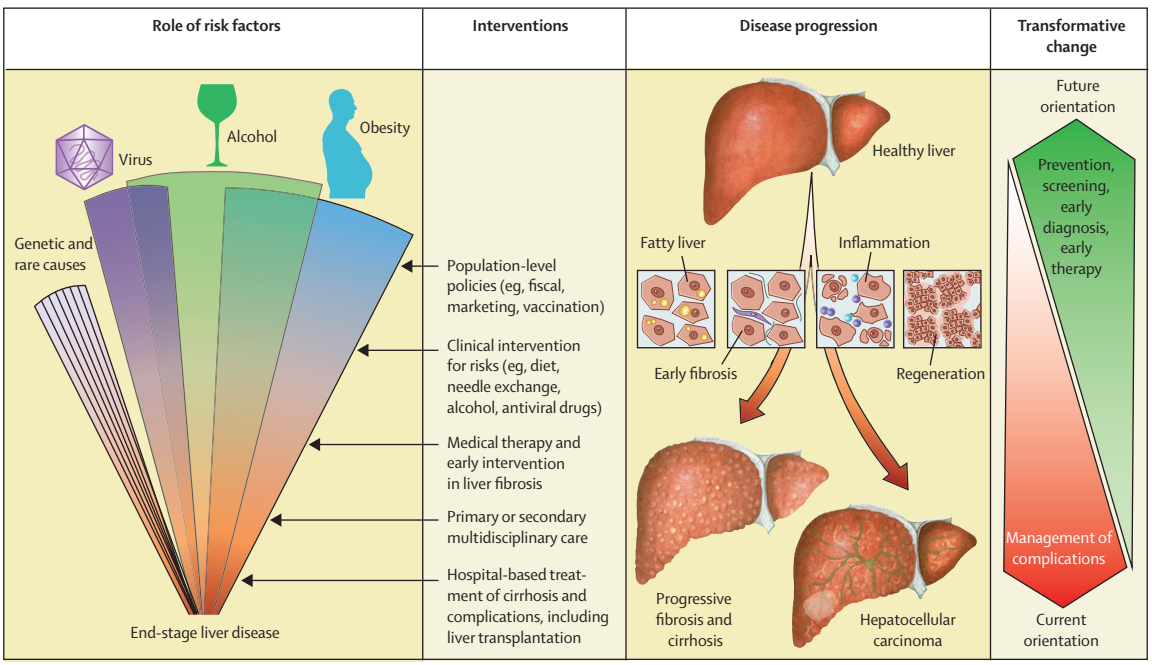

Figure 4: **Risk factors, interventions, and disease progression for different liver diseases**
Progressive liver fibrosis is the single common pathway for all causes of chronic liver disease. Liver cancer mostly develops in patients with advanced fibrosis but is increasingly observed in people without cirrhosis with non-alcohol fatty liver disease. Population-level interventions tend to be more effective and less expensive than hospital interventions. Printed with permission from Kari Toverud.

Alcohol and liver disease: a dose-related condition at the population level

Europe has the highest levels of alcohol consumption per person, the highest prevalence of heavy episodic drinking, and the lowest rates of abstention from alcohol in the world.[11,20] According to GBD modelling, alcohol was responsible for around 580 000 deaths in 2019 (6·2% of all deaths) in the WHO European region.[16] Others have estimated that alcohol causes about 40% of the 287 000 premature liver-related deaths in Europe every year, although the true number is probably higher.[21] Alcohol-related liver disease is the most frequent type of liver disease, being responsible for at least 50% of cirrhosis cases,[20] and is the most common indication for liver transplantation in Europe.[22,23] Despite this fact, research on alcohol-related liver disease is underrepresented, amounting to just 5% of all publications in the area of liver disease (2010–14 assessment). At the large European and American liver congresses, alcohol-related liver disease represented only 7% and 4%, respectively, of the research presented.[24]

Alcohol-related harm correlates with the volume and pattern of drinking, with epidemiological studies showing an exponential dose–response relationship between alcohol and liver disease.[25] As such, an understanding of the volume and pattern of alcohol consumption across populations and by individuals is essential to better understand alcohol-related liver disease and to identify the most effectual and cost-effective policies and interventions to prevent and reduce the burden of disease. For most countries in the WHO European region, there is a strong correlation between liver-related mortality rates and population-level alcohol consumption (figure 5A). Some countries, notably Ireland, have lower standardised liver-related mortality rates than might be expected from population-level alcohol consumption, but this might, in part, reflect errors in coding in relation to death certificates. There are a number of European countries with very high levels of liver-related mortality in relationship to alcohol consumption (figure 5B), which might reflect irregularities in the recording of alcohol consumption. For example, Hungary and Moldova have high levels of recorded alcohol consumption but also have high levels of unrecorded alcohol consumption,[20] reflected in the rates of liver-related mortality.

The evidence linking liver-related mortality and population-level alcohol consumption sends a crucial message for disease prevention: alcohol-related cirrhosis is a dose-related condition at the population level, and the most effectual and cost-effective means to reduce mortality rates from alcohol-related liver disease are interventions that reduce population-level alcohol consumption.[26–28]

The European landscape of viral hepatitis

Based on GBD estimates, there were approximately 300 deaths per day due to HBV and HCV in the WHO European region in 2019,[16] the majority related to cirrhosis. These GBD estimates indicate that ten of the

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See Online for appendix

For **WHO European mortality statistics** see https://www.who.int/data/data-collection-tools/who-mortality-database

For **WHO data on liver disease** see https://gateway.euro.who.int/en/datasets/european-health-for-all-database/

For **changes in liver disease morbidity and mortality** see http://ghdx.healthdata.org/gbd-results-too

For the **WHO definition of Europe** see https://www.euro.who.int/en/countries

53 countries in the region account for 74% of the total viral hepatitis burden, while some smaller countries (eg, Georgia) have the highest rates in the population.[7,16]

Robust estimates of incidence and prevalence of chronic HBV and HCV infection remain challenging even in countries with well developed surveillance systems, due

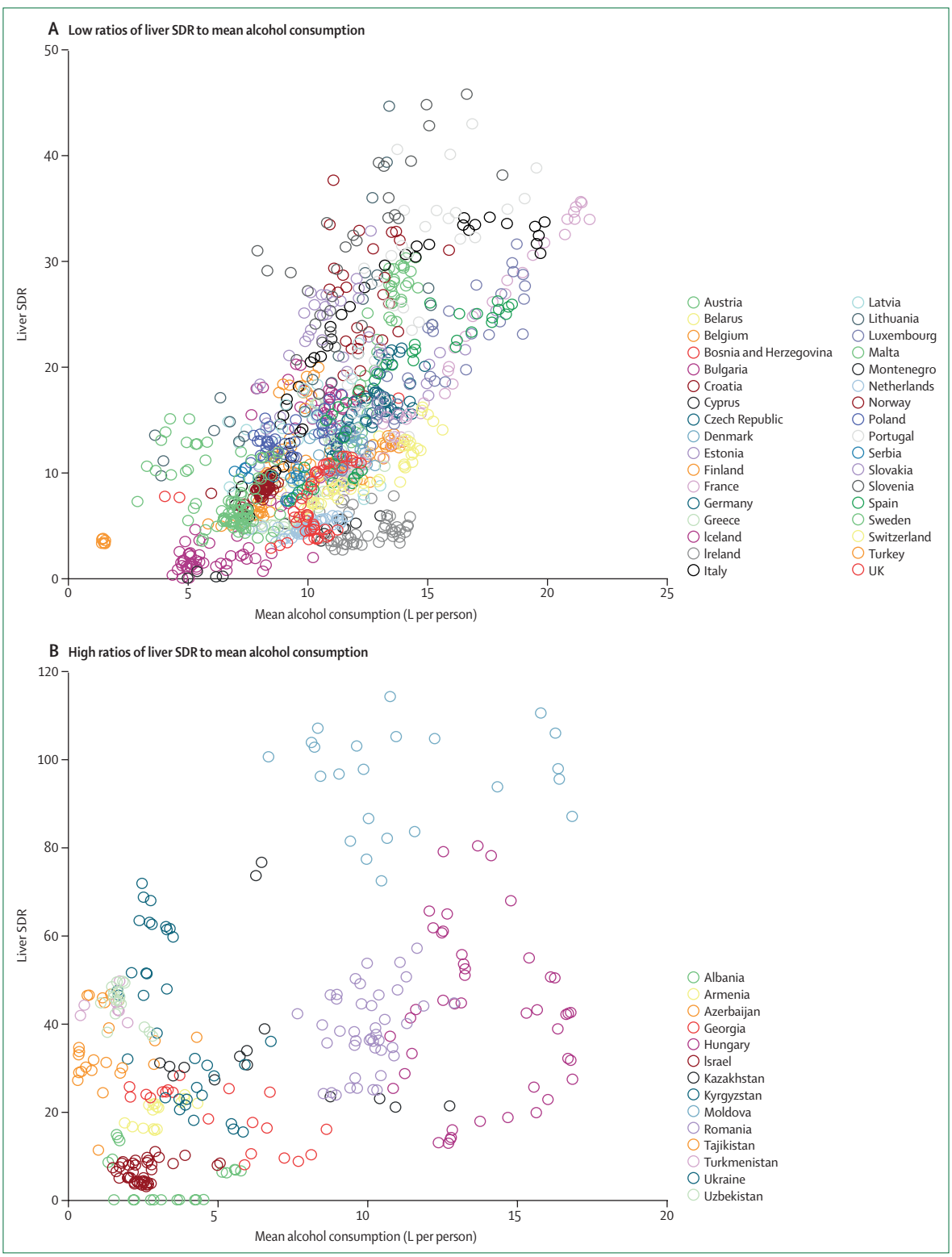

***Figure 5*: Population-level alcohol consumption and SDRs for liver disease**
(A) Countries with low ratios of liver SDR to mean yearly alcohol consumption. For many European countries, the association between alcohol consumption and liver-related mortality is self-evident, with a tight correlation between countries and temporally within countries (Spearman's correlation coefficient 0·63, p<0·0001). (B) Countries with high ratios of liver SDRs and mean alcohol consumption. Countries were selected if the maximum liver SDR divided by the alcohol-per-capita ratio is greater than or equal to 4 (Spearman's correlation coefficient 0·31, p<0·0001). Data are from the WHO Health For All 1968–2016 dataset (appendix p 12). Analysis by Nick Sheron. SDR=standardised death rate.

to the high frequency of asymptomatic and thus largely undiagnosed infections, the scarcity of formal screening programmes, and poor access to diagnostic testing. Therefore, epidemic models are often used to infer disease burden and transmission. However, absent or uncertain data underpinning these models pose methodological challenges.[29] A collaborative effort by EASL and the European Centre for Disease Prevention and Control has shown the feasibility of sentinel site surveillance—piloted in Bulgaria, Norway, and Portugal— to measure the fraction of cirrhosis and hepatocellular carcinoma attributed to viral hepatitis and help facilitate country-level monitoring, without which evaluation of the impact of interventions to avert liver disease will be thwarted.[30]

Between 1·6% and 3·1% of the population in Europe are estimated to be infected with hepatitis viruses, with prevalences ranging markedly from low (<0·1% for HBV and <0·5% for HCV) in some western, northern, and central European countries to high (6–8% for HBV and 3–6% for HCV) in some countries in eastern Europe.[31,32] WHO cites a prevalence of 1·5% (1·1–2·4), which means a total of 13·6 (10·2–22·1) million people living with HBV and a prevalence of 1·3% (1·1–1·5), which means a total of 12·5 (10·0–13·7) million people living with HCV among the general population in 2019. Service coverage and awareness remains inadequate: in the European region, it is thought that there are 2·5 (2·0–3·2) million people living with HBV who knew their diagnosis in 2019 (19% of the total) and 3·3 (2·7–4·2) million people living with HCV who knew their diagnosis in 2019 (24% of the total).[32] People who inject drugs (PWID) and people who are incarcerated have the highest prevalence for both infections.[33] The prevalence of HCV or HBV infection is 15–50 times higher in PWID than in the general population in European countries with available data, and risks associated with injecting drugs contribute to most new HCV infections in Europe.[34–37] However, transmission due to unsafe procedures inside and outside health-care settings continues to play a role in several countries.[38]

The introduction of universal childhood HBV vaccination in the 1990s was a landmark event in hepatology; this intervention has had a marked positive effect on the prevalence of HBV infection in children younger than 10 years.[39–42] There has also been a documented decrease in the incidence of hepatocellular carcinoma,[43,44] and the HBV vaccine is the first vaccine that has been shown to prevent neoplasia.[45] Although vaccination has reduced the prevalence of HBV in children, vaccination programmes will not alleviate the large existing burden of chronic HBV infection in older generations. Thus, many countries, such as Bulgaria and Romania, still have a heavy disease burden in older cohorts.[46] Furthermore, low-endemic countries in Europe with an overall HBV prevalence of nearly 1% among the general population have rates of HBV infection in foreign-born immigrants of up to 5%, contributing to an important fraction of the total number of HBV cases in these countries.[47] The 2030 goal of preventing new cases of chronic HBV infection in Europe requires widespread birth dose vaccination and additional interventions, including third trimester nucleoside analogue prophylaxis, to prevent mother-to-child transmission from mothers with viraemia.

The overall disease burden of HDV co-infection in patients with HBV is declining in Europe following the introduction of HBV vaccination programmes. The current prevalence of anti-HDV (reflecting either past or current HDV infection) is about 3% among young individuals and PWID (of those positive for HBsAg), showing the positive impact of HBV vaccination and harm-reduction programmes. Still, high rates of HDV infection are observed in older individuals in countries such as Romania and Moldova, where HDV infection is endemic. Currently, immigrants from countries with high HDV prevalence are responsible for most new cases of HDV infection in Europe.[48] Co-infection with HDV results in more rapid progression to cirrhosis and hepatocellular carcinoma,[49] but specific therapies are under development, just approved, or on the horizon.[50]

On the basis of the presence of anti-HCV antibodies or surveys done in selected populations, two-thirds of people infected with HCV in Europe live in eastern regions.[7,51] The incidence of HCV-related cirrhosis, hepatocellular carcinoma, and liver transplantation for end-stage liver disease due to HCV infection is declining due to the scale-up of treatment with highly effective direct-acting antiviral therapies.[52,53] Within 4 years of the introduction of direct-acting antivirals in Scotland, major reductions in new presentations of decompensated cirrhosis (–67%; ie, cirrhosis diagnosed after the development of complications), hepatocellular carcinoma (–69%), and associated deaths (–49%) were observed among those with chronic HCV infection.[52,54] The prevalence of chronic HCV infection is estimated to have declined, perhaps by as much as a third, in many western European countries (eg, France, Spain, Italy, and the UK) during the past 5 years, on the basis of estimates of available data and the size of at-risk populations. However, these estimates are dependent on imperfect models using incomplete surveillance data to track progress.[55] Although it is difficult to measure incidence directly (because of asymptomatic infections and suboptimal surveillance programmes), it has been suggested that the incidence of HCV infection has remained fairly stable during the past 5 years. Currently, transmission due to injection drug use accounts for 84% (95% credibility interval 57–94) of new HCV infections in Europe.[37]

Hepatitis E virus (HEV) infection is an important cause of acute viral hepatitis with an increasing incidence. However, it is underreported, as the majority of HEV infections are asymptomatic and only 20 European

	Prevalence, counts (95% UI)	Incidence, counts (95% UI)	Total years of life lost (95% UI)
NAFLD and NASH	148 000 000 (134 000 000–163 000 000)	Data unavailable	Data unavailable
Cirrhosis due to NASH (total)	862 000 (600 000–1 200 000)	44 500 (32 000–62 600)	591 000 (416 000–807 000)
Cirrhosis due to NASH (compensated)	804 000 (559 000–1 120 000)	21 000 (13 600–32 700)	Data unavailable
Cirrhosis due to NASH (decompensated)	58 400 (40 900–81 700)	23 600 (16 700–32 600)	Data unavailable
Liver cancer due to NASH	6610 (5060–8720)	5010 (3810–6610)	89 900 (69 400–117 000)

For detailed description of the methods for retrieval of estimates of case counts from the Global Burden of Disease 2019 resources, see the appendix (p 10). NAFLD=non-alcohol fatty liver disease. NASH=non-alcohol steatohepatitis. UI=uncertainty interval.

Table 1: **WHO European region epidemiology of NAFLD, NASH, and related liver disease in 2019**

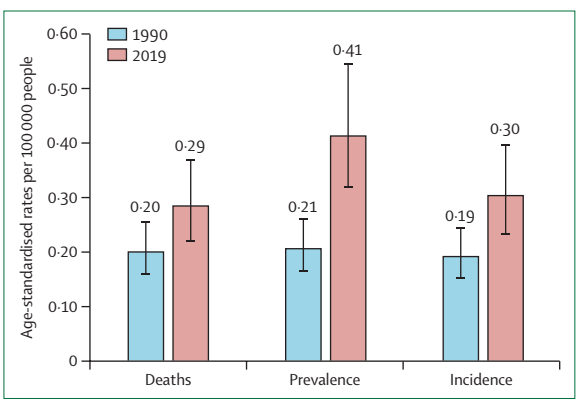

Figure 6: **Epidemiology of primary liver cancer due to NASH in the WHO European region, 1990 *vs* 2019**
Estimates are retrieved from Global Burden of Disease 2019, and are expressed as age-standardised rates per 100 000 people (appendix p 13). NASH=non-alcohol steatohepatitis.

countries actively monitor HEV infections, rendering it difficult to gauge the true incidence. Most cases of acute HEV infection occur in men older than 50 years, are caused by genotype 3, are food-borne, and usually resolve spontaneously.[56] However, it is increasingly recognised that, in immunosuppressed individuals or those with pre-existing liver disease, HEV infection can progress to chronic disease.[57]

Metabolic liver disease in Europe: an epidemic on the rise

NAFLD is becoming a leading cause of liver-related mortality in Europe and is predicted to become the leading cause of end-stage liver disease in Europe unless drastic action is taken.[58–60] Indeed, NAFLD is already the most common liver disease worldwide, affecting as much as a quarter of the global adult population, with a prevalence of 23·7% (95% CI 16·1–33·5) in Europe.[61] For people with NAFLD, the development of non-alcohol-related steatohepatitis (NASH), characterised by the presence of fat in the liver together with signs of inflammation, marks the first step of progression towards advancing stages of liver fibrosis.[62] Modelling of the disease burden in France, the UK, Germany, Italy, and Spain, along with China, Japan, and the USA, shows that the burden of advanced liver disease due to NAFLD will more than double during 2016–30.[59,63] Modelling also suggests that the annual predicted economic burden of NAFLD in Europe will be more than €35 billion in direct costs and a further €200 billion in societal costs.[64]

NAFLD is an often neglected but integral component of metabolic disturbances in people with obesity and type 2 diabetes. The prevalence of NAFLD is very high in people with obesity (75–92%) or severe obesity (>90%),[65] and was 59·7% (95% CI 54·3–64·9) in a meta-analysis of 24 observational studies including 35 599 people with type 2 diabetes.[66] In another study, the prevalence of biopsy-proven NASH among people with type 2 diabetes was 37·3% (24·70–50·02), of whom 17% (7·29–34·86) had significant fibrosis (more than stage F2, in a classification from F0 [no fibrosis] to F4 [cirrhosis]).[67] These data rank NAFLD as a major non-communicable disease (NCD), on which we will elaborate further on.

The burden of NASH in the WHO European region in 2019, the prevalence of NASH-related cirrhosis and liver cancer, and resulting estimated years lived with disability indicate that NASH affects the lives of hundreds of thousands of Europeans (table 1). The latest GBD estimates of the age-standardised death rate from NASH-related cirrhosis in the WHO European region was 1·4 (1·0–1·9) per 100 000 in 1990 and increased slightly to 1·5 (1·1–2·1) per 100 000 in 2019. Greater increases are noted during the same period in the prevalence, incidence, and mortality of NASH-related liver cancer (figure 6). Between 1990 and 2019, the age-standardised prevalence rate of liver cancer due to NASH has almost doubled.

Furthermore, a purely liver-centric view does not encompass the multisystem and multidisciplinary implications of NAFLD. Indeed, NAFLD is just one facet of a systemic disease that confers substantially increased morbidity and mortality on those patients who are affected and for which the most common causes of death are cardiovascular disease (~40% of deaths), followed by extrahepatic cancers (~20%), and liver-related complications (~10%).[68–71]

Primary liver cancer: a prototype case for screening

In 2020, primary liver cancer was the sixth most common tumour in terms of incidence and the third most lethal tumour in terms of mortality.[72] Hepatocellular carcinoma accounts for more than 80% of all primary liver cancers. Although rarer than hepatocellular carcinoma, cholangiocarcinoma, arising from the bile duct epithelium, confers an even poorer prognosis due to late diagnosis.[73,74] Only 20% of patients with cholangiocarcinoma are eligible for surgical resection, with a 5-year survival rate of less than 10% for all patients.

Within Europe, around 87 000 new cases of hepatocellular carcinoma were diagnosed in 2020, resulting in

an average age-standardised annual incidence rate of 5·2 per 100 000 person-years. During the same year, around 78 000 people in Europe died as a consequence of liver cancer. Driven by differences in aetiology and other factors, the incidence in northern Europe is around half (12 000 cases per year) that of central, eastern, southern, and western Europe (24 000–26 000 cases per year).[72] While often a sequel and accompaniment of cirrhosis from a variety of causes, NAFLD-related liver cancer stands out by increasingly being seen even in patients without cirrhosis.[75,76]

The mortality-to-incidence ratio measures the lethality of a tumour, such that, for the most lethal tumour possible, mortality would equal incidence, resulting in a mortality-to-incidence ratio of 100%. In comparison to prostate cancer, which has a high curability and a mortality-to-incidence ratio of 20%, the mortality-to-incidence ratio of hepatocellular carcinoma is 91% worldwide, ranking it as the third most lethal tumour globally.[72] The average number of years of life lost due to hepatocellular carcinoma compared to a reference population of the same age-class was estimated as 7·9 years in 2007–14,[77] although reassuringly the number of years of life lost has declined from 12·6 years in 1986–99 and 10·7 years in 2000–06. This reduction might reflect advances in the diagnosis and management of hepatocellular carcinoma but also its occurrence at later stages in life, in which comparative life expectancy is shorter.[77] Indeed, the average age of onset and death have risen over the years and are now about 68 years and 71 years, respectively, with the loss of life span closely related to the age of diagnosis. Patients diagnosed with hepatocellular carcinoma before 60 years of age might lose an average of 15·5 years of life, whereas those diagnosed after 75 years might only lose 4·5 years.

Detection of hepatocellular carcinoma at earlier stages could reduce mortality to a maximum of 5 years of life lost, regardless of age at diagnosis, but unfortunately more than 60% of patients with hepatocellular carcinoma in Europe are diagnosed at intermediate or advanced stages.[77,78] This is in contrast to Japan, where more than 60% of these patients are diagnosed at earlier stages,[79] making a strong case for surveillance for hepatocellular carcinoma in Europe.

The complex and costly care of rare liver diseases

Most paediatric liver diseases fall into the definition of a rare disease (ie, with a prevalence less than 1 per 2000). However, rare liver diseases in adults are mainly autoimmune liver diseases—ie, primary biliary cholangitis, autoimmune hepatitis, and primary sclerosing cholangitis—and genetic metabolic liver diseases, such as Wilson's disease or α1-antitrypsin deficiency and haemochromatosis. Rare liver tumours, polycystic liver disease, and other structural and vascular liver diseases also fall into this category.[80] Despite their rarity, these liver diseases account for a disproportionate number of patients in liver transplant programmes, reflecting the substantial unmet need with regards to effective medical therapies. In the European Liver Transplant Registry, rare diseases (ie, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune hepatitis, biliary atresia, Budd–Chiari syndrome, and Wilson's disease) cumulatively accounted for 20·7% of liver transplants in 2015, 21·8% in 2016, and 22·6% in 2017.

For the **European Liver Transplant Registry** see http://www.eltr.org/

The young age of presentation of many rare liver diseases poses a considerable challenge for patients and health systems, as do the ongoing health-care costs. One example is primary sclerosing cholangitis, which typically presents in people aged 30–40 years. There is no approved medical therapy for this disease and most patients require a liver transplant 15–20 years after presentation.[81] There is substantial comorbidity, as inflammatory bowel disease occurs in up to 80% of people with primary sclerosing cholangitis, and there is a high subsequent risk of developing cholangiocarcinoma and other cancers. The complex care required in the management of patients with primary sclerosing cholangitis, even before liver transplantation, is costly, with data from the Netherlands estimating the annual costs per patient at around €12 000. This amount translates to more than €600 million every year across Europe, exemplifying how, despite their rarity, rare liver diseases are important drivers of health-care costs due to their substantial morbidity, early onset, and chronicity. Furthermore, decreased quality of life, substantial early mortality, and loss of quality-adjusted life years (QALYs) add to the high disease burden.

Medical and surgical advances mean that children and young adults with rare liver diseases mostly survive with good quality of life into adulthood.[82–85] This requires appropriate transition from paediatric to adult care, with the growing population who require a liver transplant representing a patient group in itself. One example is biliary atresia, which is the single most common cause of neonatal liver disease (with an incidence of one per 19 000 neonates or about 270 new cases per year in Europe) and the most frequent indication for liver transplantation in children.[82,83] Only 25% of all patients with biliary atresia reach adulthood with their native liver, and 45% of the 600 paediatric liver transplants every year in Europe are for biliary atresia. Calculated on the basis of the Diagnostic Related Grouping system, a patient with biliary atresia having a good outcome costs about €27 000 within their first 10 years of life. By contrast, the costs for a patient with an unfavourable course and who requires an early transplantation are 11 times higher.[86,87] Early diagnosis and cost-saving therapies can be achieved by establishing effective case-finding procedures, standardised treatment protocols, and centralisation of patients to high-volume paediatric liver units.[88]

The challenges of drug-induced liver injury

Drug-induced liver injury (DILI) is the main cause of pre-marketing and post-marketing withdrawal of drugs[89] and is of great regulatory concern. DILI results from the inherent hepatic metabolism of a wide range of compounds.[90,91] From a clinical perspective, DILI is an extremely challenging condition due to the many drugs used in clinical practice, the many herbs and dietary supplements with hepatotoxic potential, and the variable clinical presentation that spans most pathological liver manifestations, from fatty liver and inflammatory and cholestatic features to severe, acute liver failure with high mortality.[92] Specific biomarkers have not been found,[93] and diagnosis often relies on exclusion of other liver diseases and careful review of the patient's history.

The true prevalence of DILI in Europe is hard to assess.[93] The first prospective population-based study on DILI came from France in the late 1990s and found an annual incidence of 13·9 patients per 100 000.[94] The Spanish Hepatotoxicity Registry started as a cooperative network of clinicians and researchers interested in DILI, who published an analysis in 2021 based on 20 years of experience,[95] showing that anti-infectives were the most common cause of DILI and were responsible for up to 40% of DILI cases. The most common cause of acute liver failure is acetaminophen (also known as paracetamol). Causes are variable throughout Europe, with high numbers of DILI cases due to acetaminophen-induced liver failure in the UK (43%) and Scandinavia (17%) but much lower numbers in Spain (2%) and France (7%).[96] This variability is poorly understood but might be related to different over-the-counter availability of acetaminophen in different countries.

The overlapping risk landscape of COVID-19 and liver diseases

In part due to the COVID-19 pandemic, obesity is now recognised as a metabolic disease risk factor in infectious diseases beyond its traditionally accepted link with other diseases, such as type 2 diabetes and cardiovascular disease. However, obesity is increasingly recognised as a chronic disease in itself.[97] Obesity has been repeatedly shown to lead to poor outcomes in the form of respiratory failure and mortality in patients with COVID-19;[98] notably, this metabolic link explains some of the variation in COVID-19-associated mortality across different ethnic and socioeconomic groups, in part mirroring differences in the prevalence of obesity and type 2 diabetes according to ethnicity and deprivation.[99–102]

A meta-analysis has also shown that NAFLD was associated with a doubling of the risk for severe COVID-19, independent of obesity, although these findings need further confirmation and elucidation.[103,104] The COVID-19 pandemic provides an important opportunity to heighten current awareness of metabolic risk factors, raise public awareness of the risk of obesity-related conditions, and drive policy action to reduce the prevalence and improve the prevention and treatment of obesity.

Synergies and the multiplicative harm of liver disease risk factors

The risk factors for liver disease interact with, and are amplified by, one another, rather than merely being additive. Many of the negative outcomes of both unhealthy alcohol use and liver disease are due to their interactions with other factors, including socioeconomic status.[105] Although having obesity with related comorbidity and unhealthy alcohol consumption each separately increase the risk of liver disease, the combination of these risk factors leads synergistically to an even greater risk of liver disease.[106–108] Having obesity makes alcohol consumption far more dangerous; a body-mass index (BMI) of more than 30 kg/m² doubles the hepatotoxicity of alcohol.[106] Alcohol use and obesity also combine synergistically to increase the risk of hepatocellular carcinoma (7 times greater risk if both risk factors are present versus none).[108] In a large study, concomitant metabolic syndrome increased the 10-year risk for advanced liver disease from 0·3% to 1·4% for moderate alcohol consumption and from 0·8% to 2·4% for unhealthy alcohol consumption.[109] The two risk factors coexist in European countries (figure 7A), and grouping together countries that have both high alcohol consumption and high obesity prevalence reveals an increased liver-related mortality compared with countries with only one risk factor or none (figure 7B). Genetic modifiers act in a similar way, with milder changes to α1-antitrypsin resulting from genetic variants not causing liver disease per se, although they might enhance susceptibility to progressive forms of other liver diseases as well as hepatocellular carcinoma.[111]

There are also important liver synergies between alcohol consumption and viral hepatitis. Unhealthy alcohol consumption increases the risk of mortality from co-existent HCV infection;[112] in Scotland, the alcohol-attributable proportion of cirrhosis cases in people with HCV is between 30% and 50%.[113,114] The question of attributable risk for liver disease is, however, problematic, as a result of the poor quality of both coding aetiology and the underlying data, as discussed previously. The proportion of liver disease without a coded aetiology varies considerably by country (from 8·5% in Finland to 97% in Bulgaria); taking into account the missing data on aetiology, the proportion of alcohol-related liver disease in Europe is likely to be between 50% and 80%.[21]

Smoking might combine synergistically with other risk factors to accelerate liver disease progression.[115–117] Heavy smoking (at least 40 pack-years) and moderate drinking (80–210 g per week) led to an 85% increased chance of having NAFLD compared with people who neither

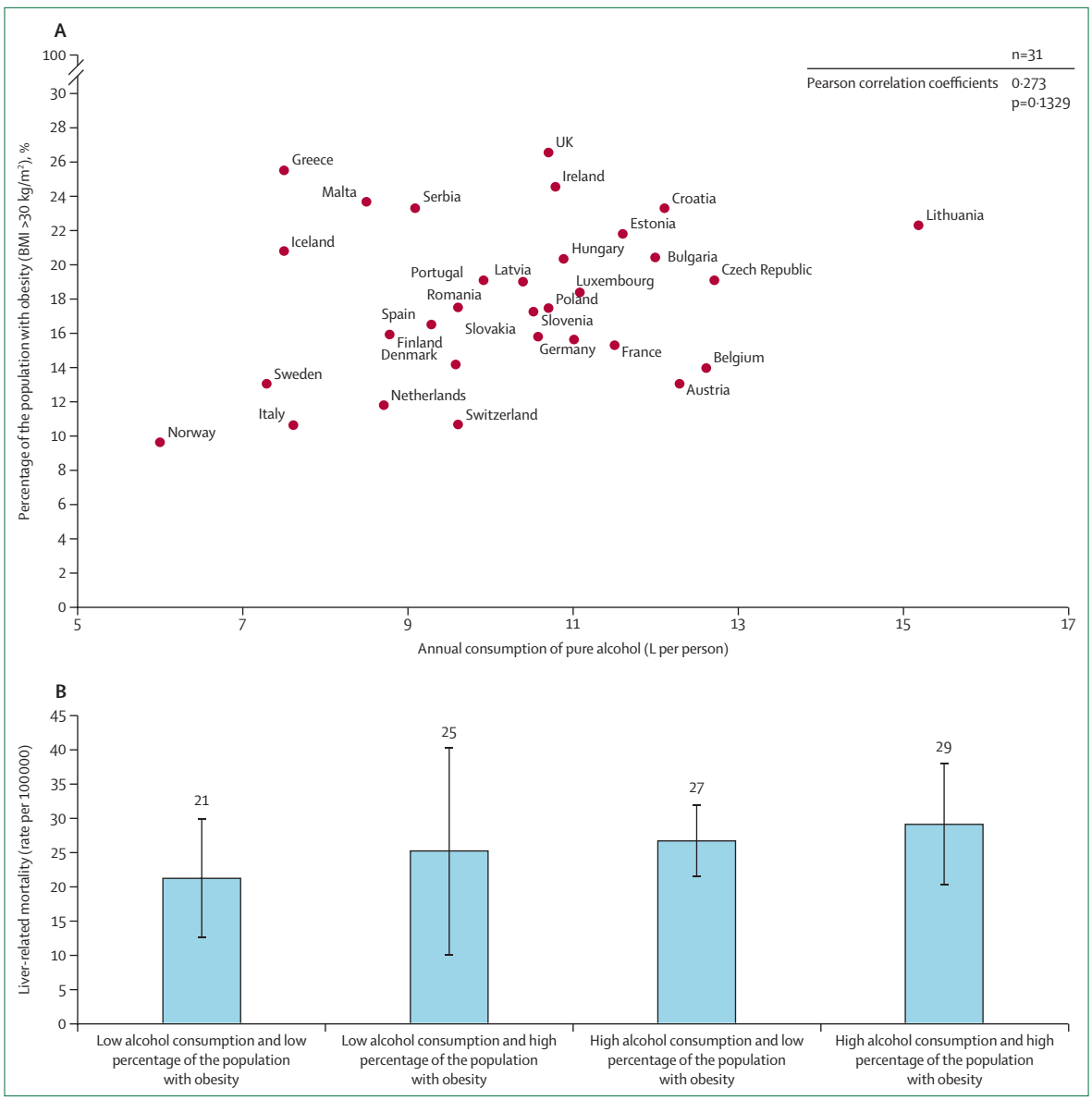

Figure 7: **Obesity, alcohol consumption, and liver disease in Europe**
(A) Coexistence of risk factors in Europe—ie, alcohol consumption per capita and obesity prevalence.[110] Data are presented on alcohol consumption and BMI from the most recent year with available data in each country (n=31). (B) Grouping together countries that have both high alcohol consumption and high obesity prevalence, countries with only one risk factor, and countries with neither. The cutoffs for the definition of high obesity prevalence and high alcohol consumption were above sample medians; median alcohol consumption was 10·5 L per capita and median percentage of population with obesity was 17·5%. Countries with low alcohol consumption and a low percentage of population with obesity included Denmark, Finland, Italy, Netherlands, Norway, Slovenia, Spain, Sweden, and Switzerland. Countries with low alcohol consumption and a high percentage of population with obesity included Greece, Iceland, Latvia, Malta, Portugal, Romania, and Serbia. Countries with high alcohol consumption and a low percentage of population with obesity included Austria, Belgium, France, Germany, Poland, and Slovakia. Countries with high alcohol consumption and a high percentage of population with obesity included Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Ireland, Lithuania, Luxembourg, and the UK. BMI=body-mass index.

smoked nor drank alcohol.[118] More clinically significant is the association between smoking and progression to fibrosis in patients with NAFLD;[119,120] a large cohort study consisting of people with type 2 diabetes reported that smoking was associated with a 60% increased risk for severe liver disease (defined as a diagnosis of hepatocellular carcinoma, cirrhosis, decompensation of cirrhosis, liver failure, or death due to liver disease).[121] Finally, smoking is also an important risk factor for the development of hepatocellular carcinoma,[122,123] with a meta-analysis showing a 50% increased risk for current smokers (independent of alcohol consumption) compared with people who never smoked.[124] There are liver synergies between alcohol and smoking such that

there is a multiplicative effect of heavy smoking and unhealthy alcohol use in the development of hepatocellular carcinoma: the combination results in an approximately ten times increase in hepatocellular carcinoma risk.[125] Unhealthy behaviours tend to stick together; for example, in the study cited previously, 64·7% of alcohol users with a BMI of at least 30 kg/m² were current smokers.[108]

Unhealthy diet is a fourth synergistic risk factor, increasing the burden of liver disease and other chronic diseases. Many European countries have seen a striking increase in the consumption of ultra-processed foods, which are often characterised by low nutritional quality, high energy density, and the presence of additives. Common examples are carbonated drinks, packaged snacks, breakfast cereals, instant sauces, and many ready-to-heat products.[126,127] In the ten countries participating in the European Prospective Investigation into Cancer and Nutrition study, processed foods contributed between 61% and 79% of mean energy intake.[128] The average content of protein, fibre, vitamins, and minerals in the diet decreases considerably with the increase in energy intake contributed by ultra-processed foods, whereas carbohydrate, added sugar, and saturated fat content increases.[129] Ultra-processed foods contribute most of the energy intake from added sugars, with added sugar content being 5 times higher than in unprocessed or minimally processed foods.[130] In the UK National Diet and Nutrition Survey (2008–14), ultra-processed foods accounted for 56·8% of total energy intake and 64·7% of total free sugars in the diet, with 61·3% of participants exceeding the recommended limit of 10% energy from free sugars.[131] Several studies across a range of populations have shown an association between the dietary share of ultra-processed foods and the risk of mortality and various diet-related chronic diseases, including obesity, type 2 diabetes, cardiovascular disease, cancer, and NAFLD.[132–139]

For the **Strategic Public Health Planning for NCDs model** see http://oecdpublichealthexplorer.org/ncd-doc/

Concurrent obesity, type 2 diabetes, and NAFLD might inhibit the reversal of liver fibrosis after curative HCV therapy, and patients cured of their HCV infection thus require monitoring and a holistic treatment approach if there is an ongoing risk of NAFLD.[140] The synergistic nature of liver disease risk factors and both the significantly greater harm this predisposes people to and the socioeconomic patterning of the risk behaviours that drive them have major implications for policy. As discussed further on in this Commission, it is important to address social determinants of health that drive relevant inequities, and factors such as price, availability, and marketing across all harmful commodities in concert.

Key policy deficits as risk factors for liver disease

COVID-19 has shown the need for public health action and the direct links that exist between population-level interventions, inequities, and mortality.[141,142] Arguments often made to oppose such interventions have been refuted by the constant publishing of data showing their effectiveness in real time.[143,144] With regards to alcohol, the evidence for equitable public health policies is remarkably consistent, summarised by WHO as best buys: tax increases on alcohol-containing beverages, comprehensive restrictions and bans on alcohol marketing, and restrictions on the availability of retailed alcohol (figure 8).[27]

In Russia in the 1980s, alcohol control policies led to a pronounced fall in alcohol-related mortality, with 1·2 million lives saved in the 5 years since the inception of the policy.[145] However, subsequent relaxation of these policies in the early 1990s sadly led to a rapid rise in mortality (appendix p 32). The maximal impact on all-cause mortality occurred within 2 years, which, given that cirrhosis develops over many years, might seem surprising, but in practice, people with liver disease frequently die as a result of acute on chronic liver failure related to recent drinking.[146] The most recent population-level policies—ie, increased taxation and a minimum sales price on alcohol—have resulted in a reduction in all-cause mortality of 39% in men and 36% in women.[147]

Modelling the effect of health policy on liver disease mortality and morbidity

The Organisation for Economic Co-operation and Development (OECD) has developed a microsimulation model to examine the relative merits of policies for NCDs. Their model consolidates previous OECD modelling work into a single platform to produce a comprehensive set of key behavioural and physiological risks. As part of this Commission, the OECD did several specific analyses of liver metrics from the Strategic Public Health Planning for NCDs model in selected European countries (the EU27 plus Switzerland, Iceland, the UK, Norway, and Russia, otherwise known as the EU27+5) for the period 2020–50 (appendix pp 46–56). The modelling comprised two parts, one examining the burden of liver disease and the other the relative effectiveness of health policies.

The OECD model was able to differentiate, for the first time, between various causes of liver disease. Every year, and across the 32 countries included in the analysis, modelling found liver disease to be responsible for about 200 000 premature deaths (figure 9), which is in line with the GBD estimates. Furthermore, the model projects healthy life expectancy to be 0·4 to 1·3 years lower over the next 30 years because of deaths due to liver diseases, with 46% of the reduction as a result of alcohol consumption and 28% as a result of obesity (appendix p 33). On average, 10·5 million life years and 8·8 million healthy life years will be lost every year in the EU27+5 because of liver disease. The average annual health expenditure for liver disease in the EU27+5 countries is €4·3 billion (appendix p 34), and the impact of liver disease on the economy of the same group of countries leads to the loss of the equivalent of 5 million full-time workers per year.

Country	Per-capita alcohol consumption (15+ years)		Age-standardised cirrhosis death rates per 100 000 (15+ years)		Excise tax			Restrictions for on-premise or off-premise sales of alcoholic drinks				Legally binding regulations	
	Men	Women	Men	Women	Beer	Wine	Spirits	Hours	Days	Places	Density	Alcohol advertising	Product placement (any)
Austria	12·0	11·6	21·1	7·4	N	N	N	Y	Y	Y	Y	Y	Y
Belgium	11·4	12·1	14·7	6·8	Y	Y	Y	N	N	N	N	N	Y
Croatia	11·2	8·9	30·1	7·3	Y	N	Y	N	N	N	N	Y	Y
Cyprus	11·3	10·8	9·5	2·7	Y	N	Y	Y	Y	Y	Y	Y	N
Czech Republic	14·0	14·4	21·7	8·9	Y	Y	Y	N	N	Y	N	Y	Y
Denmark	10·9	10·4	15·0	6·3	Y	Y	Y	N	N	N	N	Y	Y
Estonia	12·4	11·6	31·3	11·7	Y	Y	Y	Y	N	Y	N	Y	N
Finland	12·6	10·7	27·6	9·1	Y	Y	Y	Y	Y	Y	Y	Y	Y
France	12·2	12·6	14·9	5·1	Y	Y	Y	Y	N	Y	Y	Y	Y
Germany	12·9	13·4	18·9	7·8	Y	N	Y	N	N	N	N	Y	Y
Greece	10·4	10·4	8·8	2·4	Y	Y	Y	N	N	N	N	N	N
Hungary	20·1	5·0	19·1	4·5	Y	N	Y	N	N	Y	N	Y	N
Ireland	12·3	13·0	9·2	4·6	Y	Y	Y	Y	Y	Y	Y	Y	Y
Italy	7·0	7·5	11·1	5·5	Y	N	Y	Y	N	Y	N	Y	Y
Latvia	11·6	12·9	28·0	13·0	Y	Y	Y	Y	N	Y	N	Y	Y
Lithuania	15·1	15·0	39·3	15·9	Y	Y	Y	Y	N	Y	N	Y	Y
Luxembourg	12·6	13·0	16·3	6·7	Y	N	Y	Y	N	N	Y	Y	N
Malta	7·0	8·1	7·4	1·3	Y	Y	Y	Y	N	N	N	Y	Y
Netherlands	10·4	8·7	5·8	2·9	Y	Y	Y	N	N	Y	N	Y	Y
Poland	11·4	11·6	24·1	8·3	Y	Y	Y	N	N	Y	N	Y	N
Portugal	13·5	12·3	18·6	4·1	Y	N	Y	Y	N	Y	N	Y	Y
Romania	15·0	12·6	51·8	22·9	Y	Y	Y	N	N	Y	N	Y	Y
Slovakia	11·9	11·5	40·9	12·7	Y	Y	Y	N	N	Y	N	Y	Y
Slovenia	11·5	12·6	31·2	8·7	Y	N	Y	Y	N	Y	N	Y	Y
Spain	10·5	10·0	12·8	4·1	Y	N	Y	Y	N	Y	N	Y	N
Sweden	9·5	9·2	8·4	4·2	Y	Y	Y	Y	Y	Y	Y	Y	Y
UK	12·3	11·4	14·7	7·9	Y	Y	Y	Subnational				N	N
EU average	12·0	11·2	20·5	7·5	2·6/3			2·2/4				1·6	2

Figure 8: **Per capita consumption, liver cirrhosis death rates, and alcohol policy implementation in the EU and UK**
For per-capita consumption and cirrhosis mortality, countries with a rate larger than 1 SD from the EU mean are indicated by red cells, whereas countries with a rate smaller than 1 SD from the EU mean are indicated in green. For policies, a graded scale from green to red is used, with green indicating best policy implementation, amber moderate policy implementation, and red poor policy implementation. The figure was created on the basis of data from WHO.

For **WHO data on alcohol consumption and liver-related mortality** see https://www.euro.who.int/en/health-topics/disease-prevention/alcohol-use/data-and-statistics/alcohol-country-fact-sheets-2019

The opportunity for financial gains from policy implementation

The OECD model also showed the relative effect of health policies on liver disease outcome metrics, including years of life lost, disability-adjusted life years (DALYs), health expenditure, and increased labour force productivity due to a healthier and more productive workforce. The most effective measure to improve population health was food reformulation, which entails a 20% calorie reduction for foods high in sugar, salt, calories, and saturated fats, following the implementation of a comprehensive package of interventions closely followed by alcohol price policies (ie, taxation and minimum unit pricing; figure 10A). The potential societal economic gain from implementation of all the seven policies included in the analysis amounted to more than €31 billion, of which 30% was related to a reduction of health expenditure and 70% to increased labour force productivity (figure 10B). At the population level, the yearly benefits in terms of life years and DALYs was more than 1·4 million and 2·2 million, respectively, across the 32 countries included in the analysis. Furthermore, food reformulation, tax increases, and a minimum unit pricing for alcohol have implementation costs that are lower than the corresponding benefits in reduced health expenditure and increased labour force productivity. Alcohol taxes also generate revenues.

An economic modelling analysis undertaken for this Commission (figure 11A), adapting a published global model,[148] indicated HCV elimination in Europe will not be achieved without the scaling up of testing, treatment, and prevention interventions (appendix pp 57–72). HCV elimination requires a very high coverage of testing (100% diagnosis rates by 2030 and 59% of infected people treated) and expanded harm-reduction (an increase from 12% to 40% of PWID on opioid substitution therapy and from 11% to 50% with high needle and syringe programme coverage among PWID). The elimination scenario was estimated to cost €38·6 billion between 2020 and 2030 (€15·0 billion for testing, €17·8 billion for treatment, and €5·8 billion for health care related to HCV disease), plus €14·9 billion for broader harm-reduction services. Compared with the status quo, this was an additional €18·9 billion investment in HCV services and €11·1 billion for harm reduction over

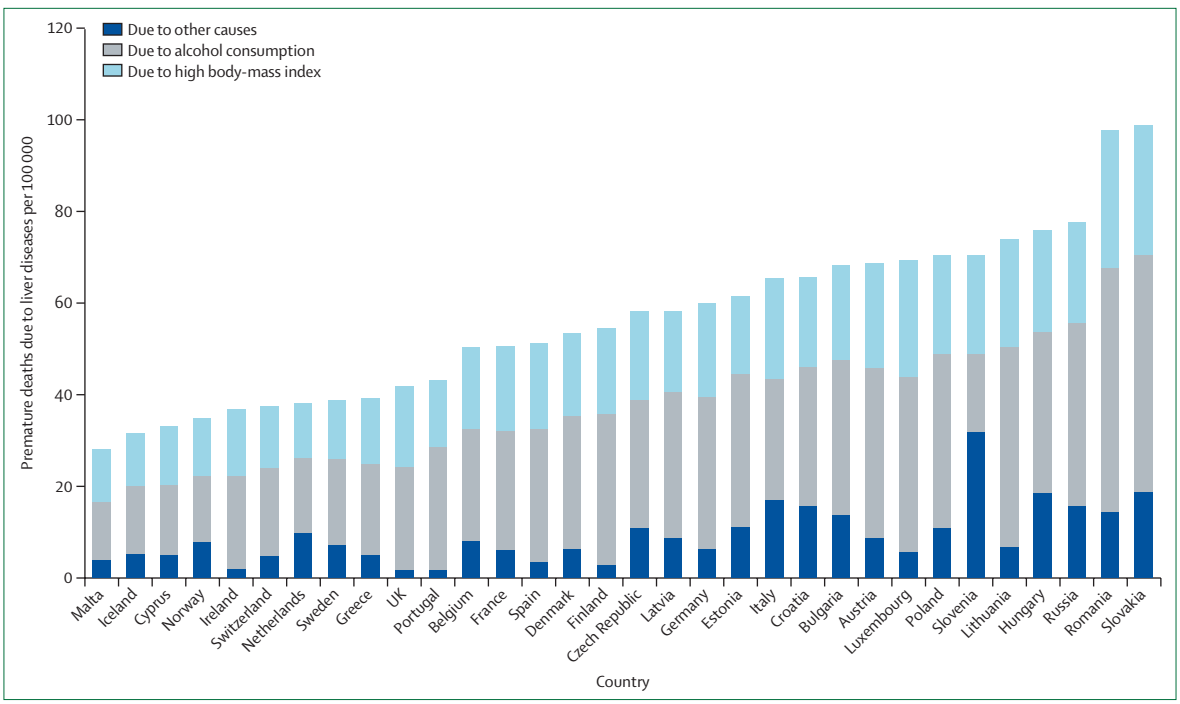

Figure 9: **Premature deaths due to liver diseases, average 2020–50**
Premature deaths per 100 000 people per year due to liver disease according to cause, calculated by the Organisation for Economic Co-operation and Development Strategic Public Health Planning for non-communicable diseases model (appendix pp 46–56).

10 years. A substantial and sustained investment in harm reduction, alongside investments in HCV testing and treatment, is important and has broader benefits than just HCV elimination, including HIV prevention and a reduction in overdoses and other non-HCV injection-related diseases, thus improving the investment case beyond that estimated here.

Achieving elimination was estimated to lead to productivity gains between 2020 and 2030 due to decreased rates of absenteeism (HCV-related sick days) and presenteeism (people attending the workplace but being less productive as a result of their illness), and a reduction in premature deaths (figure 11B). Hence, the elimination package was estimated to be cost-saving by 2033 and have a net economic benefit of €95 billion by 2050 (figure 11C). If the cost of direct-acting antivirals was €5000 rather than €2000, this would add 4 years to the time required for the programme to become cost-saving, highlighting the importance of negotiating for affordable pricing for direct-acting antivirals. Another crucial component to achieving HCV elimination is movement of treatment from the tertiary to the primary care or community settings to help ensure that countries have the capacity to treat the increased numbers required. In addition, there is increasing evidence that providing treatment in primary care or community settings increases retention in the care cascade and is cost-saving compared with treatment in tertiary settings.[149–152]

Inequalities and the next generation of patients with liver disease

Liver diseases are intertwined with social and health inequalities. Socially disadvantaged groups and underserved communities are disproportionately affected by liver disease for a multitude of reasons, including exposure to unhealthy physical, social, and economic environments; cultural factors; low levels of agency to adapt behaviours;[153] mental health issues; use of food, drugs, or alcohol to respond to psychosocial stress; and immigration, including refugees escaping from areas of high prevalence of viral hepatitis. Mortality from alcohol-related liver disease is substantially greater for disadvantaged socioeconomic groups, particularly for younger patients, resulting in major health inequalities.[154] For example, in the UK, more deprived areas have a higher rate of liver disease mortality (figure 12); rates in Blackpool (42·7 per 100 000) are more than 5 times higher than rates in Eden (8·2 per 100 000). On a European scale, the wide variation in liver transplant rates throughout Europe reflects inequalities in access to a liver transplantation programme as much as variation in liver disease prevalence (appendix p 35).

Lower socioeconomic status is also associated with a higher prevalence of liver disease risk factors. There are several pathways to explain how different factors interact at the individual and population levels to generate inequities that influence the health status of women and men in a given population: discriminatory values, norms,

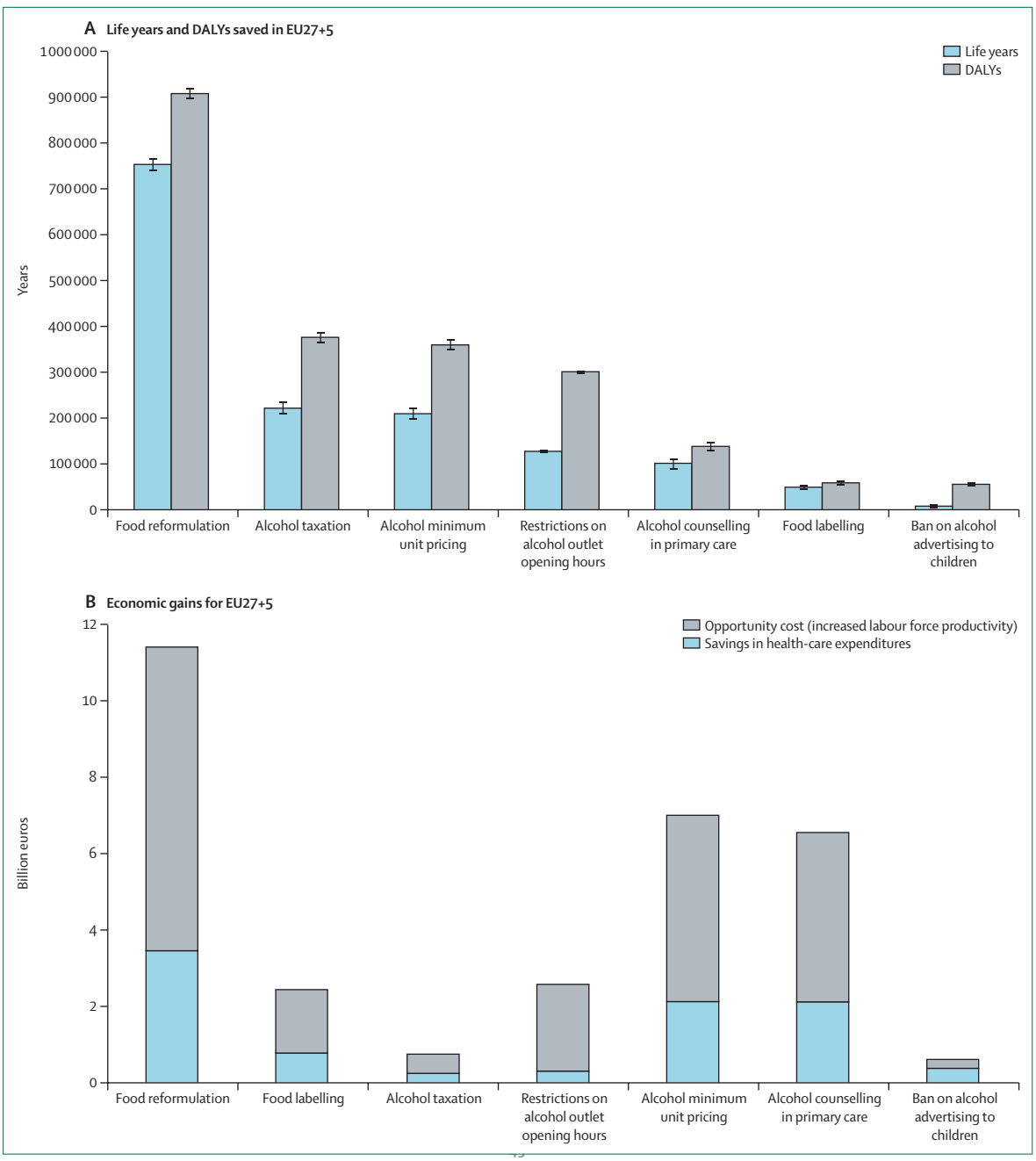

Figure 10: **Health and economic impact of different health policies**
(A) Potential average benefits of different health policies in terms of life years or DALYs per year in the EU27+5 (ie, EU and Switzerland, Iceland, the UK, Norway, and Russia), calculated by the OECD SPHeP-NCD model. (B) Potential economic impact of different health policies in terms of reduced health expenditure and increased labour force productivity in the EU27+5 calculated by the OECD SPHeP-NCD model (appendix pp 46–56). DALY=disability-adjusted life year. OECD SPHeP-NCD=Organisation for Economic Co-operation and Development Strategic Public Health Planning for non-communicable diseases.

practices, and behaviours in relation to health within households and communities; differential exposures and vulnerabilities to disease, disability, and injuries; biases in health systems; and biased health research.[156]

For example, substantial differences exist in Europe concerning the proportion of adults with overweight or obesity according to region, sex, and socioeconomic background. These differences are much more marked in women than in men, as regards both socioeconomic status and education level. The prevalence of both obesity and diabetes was higher among adults with lower socioeconomic status in 2017, indicated by lower household economic capacity in most European countries (figure 13). It has been suggested that low

For **data on the proportion of adults with overweight or obesity** see https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Overweight_and_obesity_-_BMI_statistics

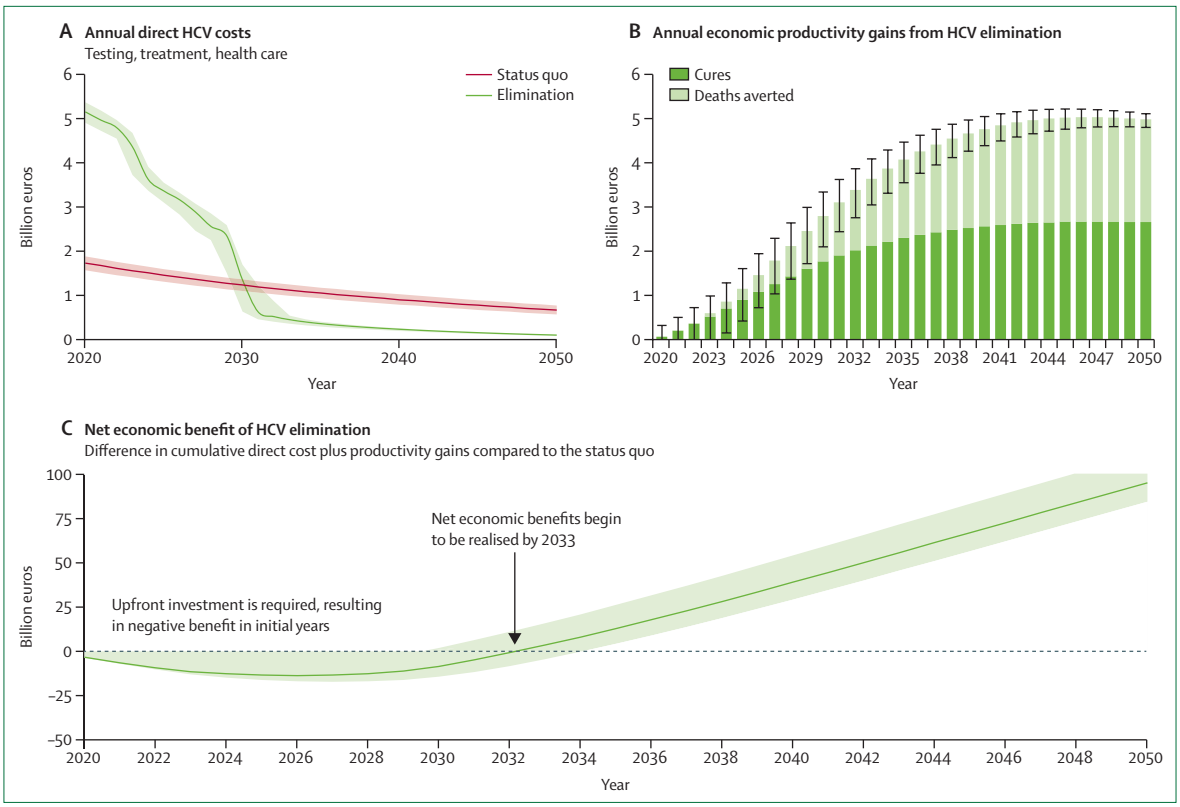

Figure 11: **Investment and return on investment from HCV elimination in the WHO European region, 2020–50**
(A) Cost of testing, treatment, and health care for elimination and status quo scenarios. (B) Annual economic productivity gains from elimination compared to the status quo. (C) Net economic benefit of hepatitis C elimination compared to the status quo (includes testing, treatment, health care, and productivity costs). Costs and disease-adjusted life years discounted at 3% per year. Solid line and shading represent median and IQR of multiple uncertainty simulations (appendix pp 57–72). HCV=hepatitis C virus.

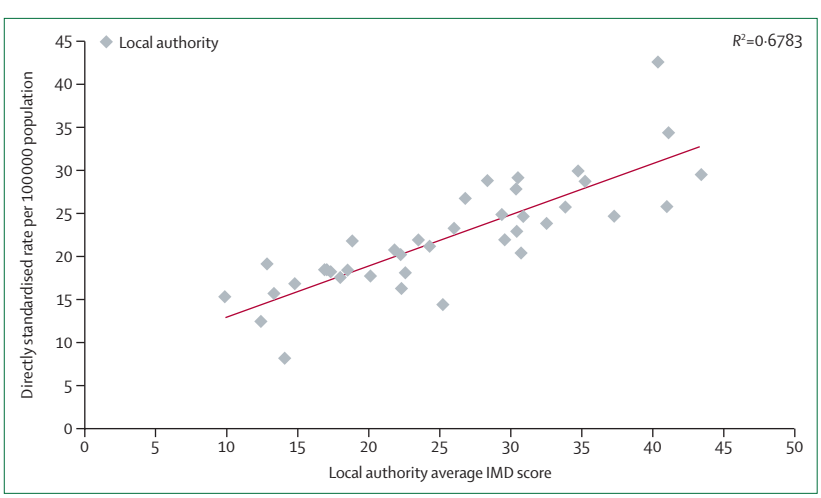

Figure 12: **Mortality rates for all liver disease (underlying cause) by local authority in northwest England and IMD score, 2006–10**
There is a strong positive association between deprivation and liver disease mortality, with the R^2 value suggesting that 68% of the total variability can be explained by deprivation. Data are from the Office of National Statistics.[155] IMD=index of multiple deprivation.

income and food insecurity might be related to increased prevalence of NAFLD and advanced liver fibrosis, most probably because food insecurity is related to the affordability of energy-dense, high-fat, high-sugar, ultra-processed foods.[157]

Children: the next generation of patients with liver disease

Childhood obesity and NAFLD represent a second wave of metabolic liver disease that will hit Europe over the coming decades. It is important both because of its direct impact of overweight and obesity in childhood, but also the tracking of childhood obesity into adulthood and through the life course. Present day adults in middle age with NAFLD are from a generation that was mostly normal weight in childhood, whereas many children nowadays risk spending the majority of their lives overweight. There is a growing appreciation that NAFLD is an early-onset condition that is likely to increase future liver-related complications, and it is now the most rapidly increasing reason for referral to paediatric hepatology centres. Evidence both from specialist liver centres and at a population level shows that children and young people with obesity have increased liver-related mortality later in life.[158,159]

Socioeconomic inequalities and childhood obesity

There is a particularly strong link between family socioeconomic inequalities and childhood obesity. In England,

the prevalence of childhood obesity more than doubles between the least deprived and the most deprived deciles of socioeconomic status, and these inequalities are growing. The Health Behaviour in School-aged Children survey highlights sex-related and socioeconomic inequalities among adolescents aged 11, 13, and 15 years. The 2017–18 survey report presents data from more than 220 000 young people in 45 countries and regions in Europe and Canada; one in five adolescents (21%) had overweight or obesity.[160] The difference in the prevalence of obesity between the most and least affluent children has grown substantially between 2014 and 2018 in most countries, with strong socioeconomic inequalities being observed such that more affluent boys and girls were less likely to have overweight or obesity. Of note, the prevalence of overweight and obesity increased in up to a third of countries or regions between 2014 and 2018. There are differences in the prevalence of childhood obesity between countries in Europe, with increasing prevalence from north to south within the region.[161]

There is a wide variation in children's diets across Europe, with a high prevalence of unhealthy dietary patterns,[162] including lower daily fruit and vegetable intake and higher added sugar intake among the least affluent than among high-affluence socioeconomic groups. Half of adolescents ate neither fruit nor vegetables daily (figure 14), whereas a larger portion of adolescents from high-affluence families ate fruit and vegetables every day than those from low-affluence families. Overall, one in six (17%) adolescents consumed sugar-sweetened beverages every day, with boys more likely to report daily consumption of these drinks than girls (18% *vs* 14%) across all ages in most countries or regions. Consumption of sugar-sweetened beverages was associated with family affluence among both girls and boys (figure 14). Physical activity is related to affluence and, in 2018, only 19% of adolescents achieved the recommended 60 min of moderate-to-vigorous physical activity daily. Physical activity participation was lower among adolescents from low-affluence families than among those from high-affluence families.[160]

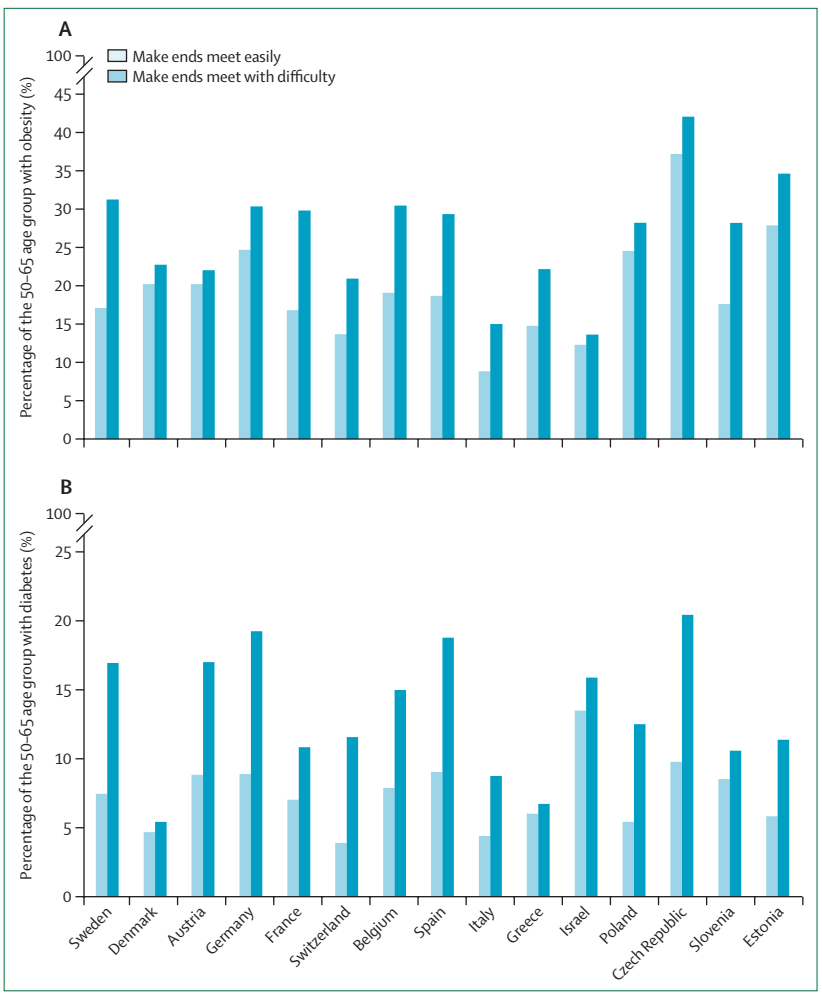

Figure 13: **Obesity and type 2 diabetes by socioeconomic status in selected European countries, 2017**
Data are from the Survey of Health, Ageing and Retirement in Europe (SHARE) showing the prevalence of obesity (A) and type 2 diabetes (B) in individuals aged 50–65 years with a low or a high household economic capacity from selected European countries in 2017. A person with diabetes was specified on the basis of a questionnaire. Obesity was defined as a body-mass index of 30 kg/m² or more. Economic status definition was based on an assessment of household economic capacity, with two potential situations: make ends meet with difficulty and make ends meet easily (appendix pp 14–15).

New marketing modalities and public health responses

Children in Europe are regularly exposed to marketing that promotes ultra-processed foods and high-energy drinks, which are rich in saturated fats, trans-fatty acids, added sugar (ie, refined sugars such as sucrose and fructose, and high-fructose corn syrup incorporated into food and beverages[163]), and salt. Such targeting of children and adolescents by food and beverage commercials, in particular those embedded in children's TV programmes, electronic media (eg, video games and DVDs), and social media, has been shown to drive consumption of high-calorie and low-nutrient beverages and foods.[164] Sugar-sweetened beverages are one of the largest sources of added sugar and an important contributor of calories with few, if any, other nutrients.[165,166] Consequently, sugar-sweetened beverage consumption is now one of the leading causes of childhood and adult obesity and associated NAFLD.[165–169]

Considering the role that social disadvantage plays on the onset and persistence of obesity and associated liver disease in children (and adults), it is essential to both address the underlying social determinants of health and adopt population-level strategies that modify the environmental drivers of behavioural risk factors, in order to relieve the human and financial costs associated with the economic, social, and health consequences of childhood obesity equitably.[170] Public health prevention and health promotion initiatives that address the environmental and commercial drivers of risk factors, such as unhealthy diets, physical inactivity, and unhealthy alcohol consumption, are important for achieving

For **more information on childhood obesity in the UK** see https://digital.nhs.uk/services/national-child-measurement-programme/

For **SHARE** see http://www.share-project.org/home0.html

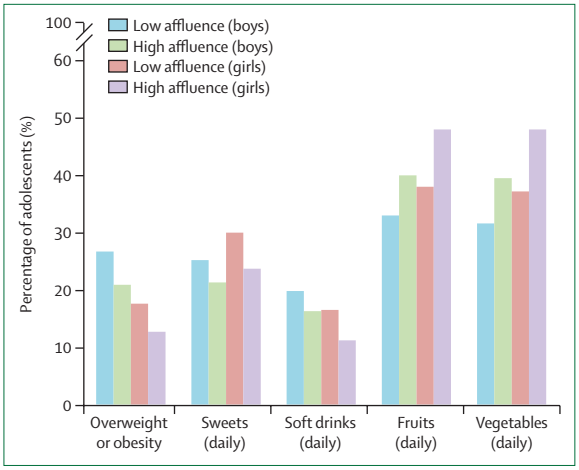

Figure 14: **Health Behaviour in School-aged Children survey in Europe**
Data are from the Health Behaviour in School-aged Children 2017–18 survey in the European region. Only the comparison between low-affluence and high-affluence categories are presented. The Pearson χ^2 test was used to examine the differences in overweight and eating behaviours between affluence categories. All p values were significant (<0·001; appendix pp 15–18).

equitable outcomes. These initiatives include interventions such as taxes on sugar-sweetened drinks that have been successfully imposed in a growing number of countries around the world and several cities within the USA.[171] Actions that target individuals, especially those that require high levels of personal agency to take effect, risk widening already stark inequities in ways that population-level action on structural factors and social determinants of health might not.[172]

Inequities resulting from European drug pricing policies: the HCV case

Health-care systems in Europe generally finance antiviral drugs for HCV through public funding or via mandatory health insurance. Access limitations, which initially restricted treatment to those with advanced disease, have been removed in many European countries.[7] Competition and price negotiations have driven costs down from the extremely high initial list prices (tens of thousands of euros), thus reducing the expenditure required in high-income and middle-income countries. However, because of the large numbers of patients infected with HCV, the costs of treatment nonetheless continue to pose substantial budgetary impacts in Europe. The vast majority of countries in Europe (48 of 53) fall into the World Bank upper-middle-income and high-income category; for many, and particularly for upper-middle-income countries such as Albania, Armenia, Bosnia and Herzegovina, Bulgaria, Montenegro, North Macedonia, Romania, Serbia, and Turkmenistan, there are no public data as to whether they have state-aided or insurance-funded treatment.

Generic HCV drugs are not generally available in Europe due to patent or licensing restrictions. The current cost of a generic HCV cure in some middle-income and low-income countries in other continents is less than €50. In Switzerland, the law allows any individual to import generic medicines provided the imported quantity is small and for personal consumption.[173] Some distrust of imported generics exists, in part because of poor knowledge of the approval process for generic drugs and fear of using substandard drugs. However, WHO prequalification ensures that prequalified drugs meet globally recognised standards.[174] This scarcity of licensed generics puts large areas of Europe in a financial dilemma with regards to HCV elimination, as a mere function of the current pricing regulations.

List prices for licensed HCV treatments are published; however, the prices actually paid are not publicly available.[175] Prices are arrived at by negotiations on a country-by-country basis and these negotiations in turn depend on budget allocations but also target treatment numbers and the consequent revenue stream guaranteed to the originators (eg, in the UK). Harmonisation of pricing will improve transparency and enhance treatment strategies. Furthermore, there are countries such as Germany where more than 100 insurance companies cover antiviral costs, leading to high cost and low transparency. In general, countries within Europe are paying lower prices than the list prices through tender competition and negotiation leverage, but these prices are unknown to the public.

Impact of COVID-19 on the burden of liver disease

The response of European countries to the COVID-19 pandemic has varied considerably, showing an underlying variability in public health capacity and policy making. Notably, the COVID-19 pandemic has disproportionately affected vulnerable communities in Europe, including immigrants, worsening inequalities.[176,177] Furthermore, since there is an intimate interplay of food insecurity, malnutrition, obesity, and advanced liver disease with COVID-19 vulnerability,[6] the pandemic has placed a spotlight on the urgent need to prevent obesity and improve diet quality in Europe.[178] Poor social conditions, which are highly prevalent in people at risk of liver disease, also increase the risk of SARS-CoV-2 infection and associated negative outcomes, as well as amplify stigma towards these groups.[179–181] In many ways, the pandemic has exposed flaws in public health; a post-pandemic Europe needs to adopt policies designed to maximise equitable actions to improve health, ranging from pooled procurement and generic drug use (including HCV therapy), to harmonised approaches to obesity prevention.

Lockdowns have led to further weight gain in many people as a result of a reduction in physical activity, unhealthy eating, and psychosocial factors (eg, boredom, anxiety, and depression).[182] Ongoing efforts from health professionals and policy makers to improve the nutritional value of European food have been opposed by the food industry, and a number of food companies have

increased their advertising and marketing of unhealthy foods and drinks during the COVID-19 pandemic.[183]

COVID-19 has threatened WHO aims for viral hepatitis elimination, with severe disruption to testing and other service provisions.[184] Modelling of the effect of delays in viral hepatitis elimination programmes due to COVID-19 suggests that, globally, a 1-year delay scenario would result in 44 800 excess hepatocellular carcinomas and 72 300 excess liver-related deaths, relative to a no-delay scenario during the next 10 years.[185] Similar models in Italy and the UK project a substantial increase in numbers of cases of advanced liver disease and deaths from HCV-related liver disease, particularly in patients with advanced fibrosis or cirrhosis.[186]

The burden of untreated viral hepatitis is substantial. Before the pandemic, only some of those infected in Europe had been diagnosed and the numbers of people living with HBV accessing treatment for viral hepatitis varied widely. WHO estimated that 210 000 (170 000–260 000) people living with HBV (2% of the total) and 250 000 (160 000–320 000) people living with HCV (8% of the total) accessed treatment up to the end of 2019.[32,187] However, diagnostic rates exceed 70% in a few countries, such as France, where long-established risk-based and population-based screening has been adopted.[188,189] Less than half of countries in the EU or EEA that responded to a 2017 survey had dedicated HBV (29%) or HCV (48%) testing guidance.[190] Access to DNA diagnostic testing for HBV remains a key barrier to identifying levels of viraemia mandating treatment. This situation leads to a proportion of individuals with chronic viral hepatitis presenting late with advanced cirrhosis or hepatocellular carcinoma.[191] The implementation of wider at-scale testing approaches across Europe, mandated by public health infrastructures, should be employed.

Widespread implementation of mass COVID-19 testing has shown that, with political will and investment, population-level screening of priority groups is feasible. These lessons can and should be applied in the context of viral hepatitis and can be useful to design and strengthen strategies to scale up testing and treatment. COVID-19 has disrupted existing viral hepatitis elimination programmes across the cascade of care at a critical juncture, with only 9 years left towards WHO target elimination goals. Quarantine and physical distancing for COVID-19 have affected screening, diagnosis, treatment, and harm-reduction programmes. The COVID-19 pandemic has hindered access to hospitals and community clinics for diagnosis and treatment; deferring HCV treatment became an almost universal practice at peaks of the pandemic. Moreover, the incidence of viral hepatitis might be increased by reducing the activity of harm-reduction centres.[192]

PWID and people who are incarcerated are key populations for viral hepatitis elimination programmes. The COVID-19 pandemic has impacted greatly on these vulnerable populations in terms of reduced access to HCV testing, diagnosis, and treatment, but also to harm-reduction programmes (eg, needle and syringe programmes and opioid agonist therapy) and critical medical services, hindering progress towards HCV elimination.[193,194] Physical distancing and quarantine during COVID-19 has increased the isolation experienced by vulnerable populations, exacerbating the already substantial harms they face, including stigma and discrimination, overdose risk, comorbidities, precarious housing, poverty, and domestic violence. Now, more than ever, these populations require timely access to harm-reduction and blood-borne virus services to prevent HCV infection or reinfection, as well as other harms associated with injection drug use.

The COVID-19 pandemic has also brought with it physical and social restrictions that might create environments that lead to increased alcohol consumption. In England, there was sustained higher purchasing of alcohol than in previous years, and this increase mainly occurred among those with an unhealthy alcohol intake before the pandemic.[195] During the same period, England saw a consistent increase in alcohol-related liver deaths, independent of the rise, fall, and rise again in COVID-19-related deaths.[196] This change in liver deaths is entirely consistent with increases in alcohol consumption predominantly impacting on those with the highest alcohol intake. The case for action for liver disease is even stronger as a result.

Stigma and discrimination of patients with liver disease

Stigma is a socially constructed phenomenon involving the devaluation of one group by another on the basis of a recognised or perceived difference. People with, or at risk of developing, liver disease frequently belong to highly stigmatised groups. These include individuals with obesity, people with alcohol use disorders, PWID, people who are incarcerated, immigrants, and men who have sex with men. There are several types of stigma (figure 15), including public stigma (occurs in the general population and is mainly associated with stereotypes), structural stigma (eg, when, at the policy level, negative labelling nomenclature is used or specific groups have less access to health and social services than other groups),[197] and health-care staff stigma (exerted by health-care professionals and often a result of stereotyping), which collectively can result in exclusion and discrimination and generate self-stigma (when a person internalises stigma). Self-stigma can ultimately result in care avoidance and lower disease awareness in these groups and subsequently worse outcomes due to late diagnosis.

Stigma is a public health, medical, and ethical issue,[198] being a consequence of health inequities as well as a key driver in perpetuating them. Stigmatising attitudes towards people with liver disease occur frequently in the general population, as there is a widespread assumption that these diseases are self-induced, coupled with an

implicit linking of alcohol-related behaviours to many liver diseases. Furthermore, there is a form of spillover of this stigma to people with liver diseases that are completely unrelated to an individual's lifestyle and behaviour; in an informal survey done by patient representatives in this Commission, among 1078 adults with autoimmune liver diseases across Europe, approximately 40% regularly faced assumptions that their liver disease was related to unhealthy alcohol consumption.

Stigma in health care: manifestations, consequences, and interventions

Stigma can take many forms, including stigmatising language, direct abuse, and discriminatory treatment against individuals. The manifestations of stigma in health-care settings have been investigated in many domains and include denial of care, provision of substandard care, and physical and verbal abuse, but also more indirect practices, such as making some patients wait longer or task-shifting their care to less experienced colleagues.[199] In many eastern European countries, for example, people with ongoing or past substance use have been excluded from HCV treatment.[200]

Within the health-care system, individuals who experience stigma might internalise it and feel mistrust towards the health-care system and a loss of self-efficacy, which might negatively affect health-care seeking behaviour[201] and result in stigma avoidance strategies, including delaying seeking care, seeking care elsewhere, not disclosing alcohol or drug use, and downplaying pain.[202,203] Ultimately, stigmatisation could lead to poorer health outcomes, which can worsen social inequalities by negatively affecting employment, social relationships, and educational opportunities.[198]

There are four main categories of interventions to address public and health-care stigma:[204] (1) providing factual information to counter prejudices and stereotypes through education campaigns or training; (2) protest (public attempts to suppress stigmatising attitudes or negative representation of the stigmatised group); (3) so-called social contact approaches, in which opinion leaders from stigmatised groups describe their condition and experiences via video or live sessions to combat stereotypes and increase empathy; and (4) the involvement of services led by peers to fight against labelling and care avoidance—eg, by helping engage people in care.

Campaigns to increase knowledge about stigmatised populations or to challenge stereotypes have generally had little impact and might even generate negative effects in terms of stigma and health-care seeking.[205] An infamous example of the detrimental effects of a campaign related to mental health occurred during the so-called Decade of the Brain (1990–2000), which labelled addiction as a brain disease.[206,207] This strategy implied that recovery is not possible and discouraged people who use drugs to seek care. A meta-analysis showed that education, and social contact programmes especially, might be more effective in reducing public stigma in adults and adolescents,[208] particularly if multitarget.[209,210] A review of interventions for decreasing stigmatising behaviour of health-care staff concluded that educational interventions resulted in improved attitudes towards stigmatised groups,[211] especially if they also rely on multi-form social contact.[212] Reduction of self-stigma is essential to reduce label avoidance, and interventions conducted by peers or community members have been shown to be effective in increasing empowerment, reducing self-stigma, and facilitating engagement in the different steps of the care cascade.[204]

Stigma towards women with liver disease manifests itself in many different ways. Research has shown that, among PWID with HCV infections, women were less likely to receive direct-acting antivirals than men were.[213] Moreover, since model for end-stage liver disease score values are underestimated in women, they also have lower chances for liver transplantation.[214–216] Among people with obesity, women are more likely to report experiences of stigma and discrimination than men are,[217,218] and gender differences have been found in the occurrence of obesity-associated disease conditions.[219] This deeper experience of stigma and discrimination among women with obesity is known to increase self-stigma and results in reduced access to and quality of health care.[220] These consequences might also be exacerbated by the prevalence of lower socioeconomic status of women with obesity with respect to men. In fact, in comparison to individuals with the highest incomes, women in the lowest income group in Europe are 90% more likely to have obesity, while for men, this figure is 50%, increasing gender-specific social inequalities.[221]

Special features of stigma in children and older people

Children and adolescents with obesity are particularly susceptible to multiple sources of weight stigma, notably in health care, schools, and traditional or social media. So-called obesogenic behaviours among children overlap with social conditions and are tightly related to old (eg, parental education and income) but also new socioeconomic risk factors (eg, small social network, immigrant status, and family structure). This overlap suggests that interventions to change behaviours in children need to comprehensively address social inequities and stigma effects.[170] Furthermore, there is a need to raise awareness of this issue.[222–225] It has been suggested that this failure to recognise and treat obesity as a chronic disease is at the heart of stigma and represents a major obstacle to seeking adequate medical management and prevention of obesity-related consequences.[97,220]

Parents of children with obesity point out the need for a radical change of terms to avoid stigmatisation of children, such as the term unhealthy bodyweight instead of obesity.[226] Childhood and adolescence are clearly

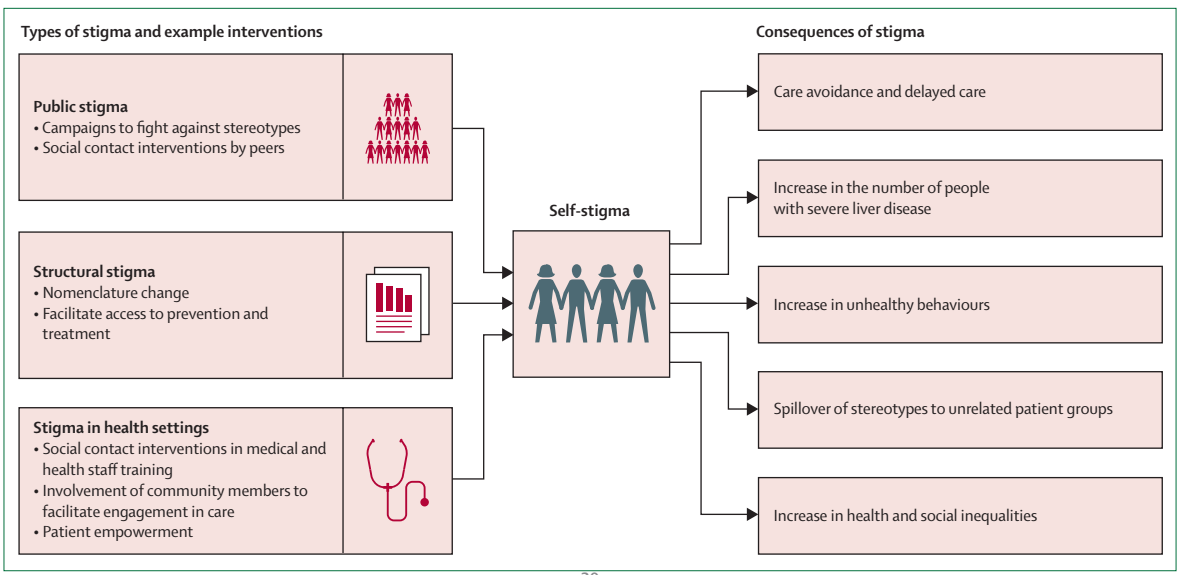

Figure 15: **Types of stigma and their consequences with example interventions**
Stigma and discriminatory attitudes towards people at risk of or with liver disease occur at different levels. To reduce the liver disease burden attributable to stigma, anti-stigma interventions should target each level and be combined. Printed with permission from Kari Toverud.

two critical periods for individuals with obesity, as they can experience weight-based victimisation through bullying.[227] This situation, amplified by stigmatisation on social media, highlights the need for greater support from parents and paediatricians alongside stronger school and social policies than exist currently.[170] In an informal query made by this Commission to paediatric liver disease specialists at 62 centres in 25 countries of the RARE-LIVER European Reference Network,[80] 50% of clinicians caring for children with liver disease felt that stigma related to liver disease was a major issue for their patients.

As people with chronic liver disease might not only age with a chronic condition but also suffer from accelerating ageing,[228,229] when seeking care, they might experience an additional layer of stigma in health settings that is related to age: so-called ageism. This consists of stigmatising attitudes from health-care staff, resulting from interactions of stereotypes, prejudice, and discrimination towards older individuals affected by ageing-related morbidities.[230] A review published in 2020 also highlighted that ageism led to worse health outcomes in older age groups than in younger age groups, and that its impact is higher in less educated older people.[231] More specifically, a European multicountry study also showed that there was a gradient in ageism, with levels rising from northwestern to southeastern Europe.[232] Effective interventions to reduce ageism are feasible and inexpensive and rely on both education and intergenerational social contact.[233]

The language of liver disease

Stigmatising language, referring especially to alcohol and substance use or excess weight and obesity, can lead to health practitioners reducing people to their condition rather than recognising their full personhood and distinct medical needs. For example, people with opioid use disorders were for years named abusers or addicts—terms linked to offences[234]—which conveys a moralistic interpretation that individuals choose to have such a disease. In addition to presupposing personal responsibility for illness, this framing can also elicit bias and discriminatory behaviours and reinforce negative stereotypes towards people with these conditions. People-first language,[235] in which the words referring to the individual are placed before words describing their behaviours or conditions (eg, PWID, people with alcohol use disorder, people with obesity) should be universally adopted.[236]

Stigmatising language is also interwoven into everyday clinical management of people with liver disease through disease nomenclature. Some efforts have been made to adjust liver disease nomenclature to reduce stigma burden in patients with liver disease. In 2015, a name change from primary biliary cirrhosis to primary biliary cholangitis was made,[237] and the EASL Clinical Practice Guidelines for the management of alcohol-related liver disease, in 2018,[238] suggested alternative terminology to be used to reduce stigmatising language. There have been similar discussions suggesting that the name NAFLD might be changed to metabolic dysfunction-associated fatty liver disease,[239–243] which was in part driven by the assumption that the term non-alcoholic in the NAFLD name was stigmatising.[244,245] Initial research has now provided early data that such a name change can improve awareness.[246,247] In this Commission, we call for a deep and comprehensive revision of potentially stigmatising nomenclature related to liver disease, including those of addiction-related and obesity-related

language. A priority in these nomenclature changes is to align with terminology proposed by affected communities—both patient groups and at-risk groups.

Moving from treatment of complications to case-finding, screening, and prevention

Unfortunately, a diagnosis of cirrhosis is often only made after an individual has developed complications of end-stage liver disease when the scope for intervention is markedly reduced. The UK *Lancet* Commission on liver disease identified that more than two-thirds of hospitalised patients had not previously been referred to a liver clinic.[12] Analysis of data derived from the CIRRUS cohort showed that early referral of patients to a liver clinic was associated with longer survival than that of patients admitted as an acute emergency (figure 16).[248] Cirrhosis is the result of progressive scarring (fibrosis) over many years or decades, the process being silent with no early signs or symptoms in most cases. It is iniquitous that a medical diagnosis in the 21st century is still made only at such late stages. Early detection is an essential prerequisite for more effective therapy and interventions to prevent progression to cirrhosis.[249]

The application of case-finding or screening for cirrhosis in Europe is variable and inconsistent, with low levels of awareness about the possible benefits of it among many health-care professionals managing patient groups at high risk of liver disease. For people with type 2 diabetes, there is an established awareness of the risks of cardiovascular disease, chronic kidney disease, and diabetic retinopathy,[250] yet there is less awareness of diabetes-related or obesity-related progressive liver fibrosis,[251,252] and there are few examples of systematic case-finding for liver fibrosis and cirrhosis. Specific therapeutic options for NAFLD are being tested in several ongoing phase 3, randomised, controlled trials, and case-finding will soon be needed for providing medical therapy and behavioural interventions.[253]

Alcohol-related liver disease is particularly neglected: out of 466 people with alcohol-related cirrhosis in a Danish cohort study, only 24% were diagnosed at the stage of compensated cirrhosis (ie, before the development of complications).[254] Moreover, it has been clearly shown that late diagnosis of chronic liver disease was associated with aetiology; the odds of a late diagnosis were 12 times higher for an individual with alcohol-related liver disease than for an individual with viral hepatitis.[255] These results point towards the crucial importance of early diagnosis as interventions become less effective and more expensive when people with unhealthy alcohol consumption have already developed cirrhosis.[26,256]

From this perspective, the range of targets of existing liver-related case-finding programmes appears too narrow. Hepatocellular carcinoma surveillance in patients with cirrhosis has shown potential benefits in observational studies.[257] HBV screening has been recommended for immigrant populations from endemic countries.[258,259] Many centres have protocols to survey for oesophageal varices in people with cirrhosis.[260] In Germany, HBV (HBsAg) and HCV (anti-HCV) testing in high-risk populations is now covered by the health-care system. Organisations such as the German Liver Foundation are advocating for an even broader implementation of liver testing, by universal alanine aminotransferase screening as part of the national general health check-up—ie, the Check-Up-35 programme. In this programme, the German health-care system finances screening tests on the basis of clinical need, scientific evidence, and cost effectiveness.

The first step of investigation of potential liver disease is commonly based on serum liver enzyme concentrations as part of generic liver blood panels, often called liver function tests or liver blood tests.[261] Liver blood tests are elevated in people with hepatitis and have historically had important roles in the detection of inflammatory liver diseases such as viral and autoimmune hepatitis. However, liver blood tests interpreted in isolation are not good correlates or predictors of advanced liver fibrosis or cirrhosis. If we are to reduce liver-related mortality resulting from progressive fibrosis, we must improve the identification of people before they present with advanced disease and the ominous consequences of hepatic decompensation. As an illustration, most people with undetected cirrhosis in the community have normal alanine aminotransferase concentrations.[262] In a community-based study in the UK, 60% of people with newly diagnosed liver fibrosis on biopsy had normal alanine aminotransferase concentrations and 91% of those with undetected cirrhosis had an alanine aminotransferase concentration within the normal range.[263,264] Similarly, in a population-based study in Catalonia, Spain, almost 75% of people with liver fibrosis, mostly due to NAFLD as assessed by increased liver stiffness using transient elastography, had normal alanine aminotransferase concentrations.[265] A considerable responsibility and opportunity resides with hepatologists in generating and communicating simple testing strategies, in keeping with the simplicity of haemoglobin A_{1c} in diabetes management or estimated glomerular filtration rate to guide chronic kidney disease management.[266]

There is now evidence to support such strategies. Optimising Delivery of Healthcare Intervention, a multicentre, randomised, controlled trial in more than 120 different locations throughout Catalonia (Spain), the UK, the Netherlands, Poland, and Sweden, has shown the benefit of providing primary health-care units with training, support, and financial reimbursement for delivering alcohol use disorders identification test-based screening and advice to screen for alcohol consumption.[267] Countries across Europe should rise to this challenge to increase the widescale rollout of a standardised liver blood test with implicit assessment of liver fibrosis, coupled with automated, laboratory reflex testing (also known as automated responsive testing) and clinical follow-up. Similar research is urgently needed for other liver disease areas. The current late diagnosis of liver

disease comes at a cost over and above the loss of life years, including the large costs of managing complications of end-stage liver disease.

The relevance of scaled-up testing for health-care costs is also evident in rare liver diseases. Only two European countries have systematic national screening programmes for neonatal liver disease (Switzerland and France initiated stool colour charts to alert parents to altered stool colour resulting from bile obstruction). As noted previously, achieving good outcomes for people with biliary atresia generates major savings in treatment costs. Extrapolated from the basis of 2700 patients per 10 years in Europe, and a 30% survival rate for those with their native liver, the financial expenses for patients with unfavourable outcomes alone are conservatively estimated at more than half a billion euros.[86,87] This scenario could be improved by 10% if early diagnosis and timely therapy could be achieved.

Liver fibrosis community screening for early detection of progressive liver disease

To reduce the burden of liver disease from alcohol and NAFLD, hepatologists, GPs, specialist nurses, or community health staff (including pharmacists) who are in contact with people at risk or patients with liver disease will need to revise their strategies. These professionals should focus on case-finding of people at risk of progressive forms of liver disease and premature death and distinguishing progressive from more benign, less rapidly progressive disease, at an early stage. The mechanisms required to do this already exist for the most part as there are cheap, simple tests for advanced liver fibrosis and cirrhosis, including a range of algorithms to calculate fibrosis risk from liver blood tests (appendix p 40), with a high degree of accuracy.[268–270]

These non-invasive tests can be used in conjunction with more specific fibrosis tests based on combinations of circulating fibrosis markers or transient elastography.[271] Elastography also has a role in identifying people with portal hypertension who need primary variceal prophylaxis and follow-up.[272,273] A fundamental flaw in current practice is that such non-invasive fibrosis tests will only be done once liver disease is already identified and hence frequently not in people with low or normal serum alanine aminotransferase concentrations. One algorithm examined more than 500 000 anonymised hospital records and found that the data required to detect cirrhosis was previously available in 96% of people who went on to have a first admission with a serious liver event.[248]

Similar fibrosis screening protocols have been examined in clinical studies, such as the Scarred Liver Project in the UK, which screened 920 people in the community with risk factors for liver disease.[263,274] Among preselected people on a risk factor basis who were identified with increased liver stiffness (assessed by transient elastography), 72% had normal liver blood tests and would be missed by traditional investigation

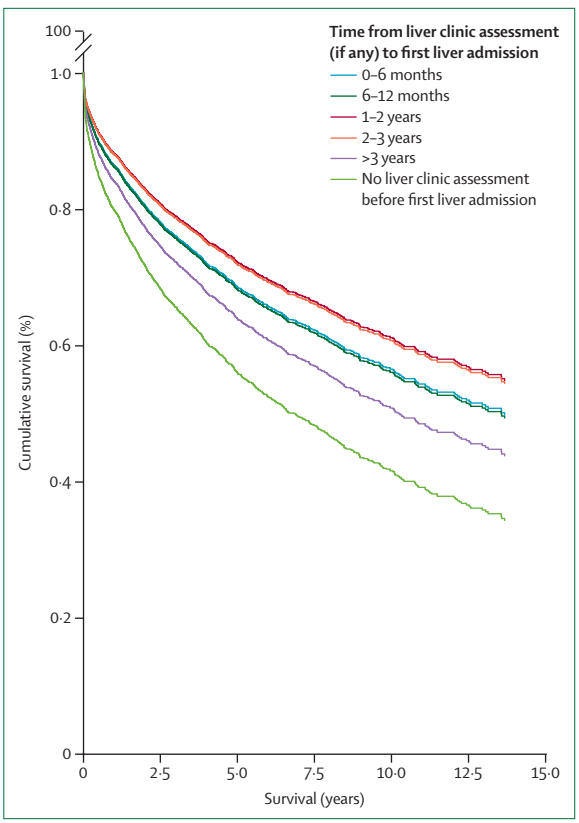

Figure 16: **Survival rates for individuals following a first admission with liver failure**

The figure shows the Cox regression survival function for first admissions with cirrhosis or liver failure. Of 3335 individuals, 2335 (70%) had not been referred to a liver clinic before the first liver admission and these individuals had a reduced survival on Cox regression analysis after considering potential confounders, such as alcohol intake, type 2 diabetes, and viral hepatitis (appendix p 18). Analysis by Nick Sheron.

algorithms. Subsequently, this diagnostic pathway has been locally adapted. Other models of case-finding were tested in the LOCATE study, which found greater effectiveness in case identification in the group based on nurse-led risk-factor identification with portable elastography assessment and referral to primary care than in the group based on regular care.[262] Two research nurses with portable elastography equipment were able to detect and stage as many new cases of progressive liver disease as five consultants in a year. Crucial to the success of this diagnostic pathway was engagement and promotion by a local GP, such that it is now in widespread use with almost as many liver fibrosis serum tests being requested by GPs as by hepatologists.[275]

In another screening project in the metropolitan area of Barcelona, Spain, out of 3076 individuals aged 18–75 years without known liver diseases and recruited randomly from the general population, 3·6% had transient elastography values of more than 9·2 kPa, values highly suggestive of significant liver fibrosis (F2 stage or greater). The most common liver disease in this cohort was NAFLD, followed by alcohol-related liver

For the **Scarred Liver Project** see https://www.scarredliverproject.org.uk/

disease. This project proposed a screening algorithm to identify silent liver fibrosis in the population on the basis of assessment of liver disease risk factors and measurement of the fatty liver index. Presence of liver disease risk factors together with a fatty liver index value greater than 60 identified 92·5% of individuals who had a high probability of liver fibrosis as assessed by a liver stiffness measurement of more than 9·0 kPa in the overall population.[265]

These examples provide strong support for the implementation of proactive testing for liver fibrosis as the crucial tool for progressive liver disease case-finding. Research should be part of such an implementation—eg, to define optimal target populations, type of tests or algorithms to be used, pathways of referral, and long-term impact of screening on liver-related mortality. In this regard, a large European study that will include 40 000 people in eight countries is underway to evaluate screening strategies for chronic liver diseases. The results of this study will help to establish the most useful case-finding strategies according to specific countries and health systems. Two such strategies have been evaluated and showed a good cost-effectiveness profile.[276,277] Nevertheless, more information is needed with respect to cost-effectiveness evaluation of screening strategies in different countries and health systems, accounting for local variability in prevalence of various liver diseases.

For the **LiverScreen study** see https://www.liverscreen.eu/

Reconsidering liver blood tests and choosing a fibrosis algorithm

The concept of liver blood tests, or of hepatic biochemistries, holds no uniform interpretation. A new analysis performed for this Commission evaluated the performance of traditional liver blood tests as predictors of future serious liver events in 400 000 patients.[248] The area under the curve (AUC) for the results before the first serious liver event for alanine aminotransferase (AUC 0·63 [95% CI 0·61–0·66]) and alkaline phosphatase (0·70 [0·68–0·71]) showed that these tests performed relatively poorly, with the best performing single test being γ-glutamyl transferase (0·79 [0·78–0·80]). The AUC for a maximum γ-glutamyl transferase result was higher (0·83 [0·82–0·84]), within the clinically useful range, but not as high as one of the dedicated fibrosis algorithms (0·91 [0·90–0·91]; figure 17).

Serum γ-glutamyl transferase concentration is frequently elevated in conjunction with unhealthy alcohol consumption. However, an elevated γ-glutamyl transferase concentration has been shown to identify both alcohol-related and other liver diseases. Serum concentrations of γ-glutamyl transferase were higher in people with an alcohol risk than in those without: the serious liver event prediction cutoff of γ-glutamyl transferase was 126 international units per L in patients with an alcohol risk compared with 79 international units per L in patients without an alcohol risk and 82 international units per L in people with type 2 diabetes. γ-Glutamyl transferase is the best single liver enzyme for predicting a future liver event, providing the correct cutoff values are used (appendix p 36). In fact, the insurance industry already commonly uses γ-glutamyl transferase as a cost-effective marker to exclude clients at risk for liver-related morbidity and mortality.

Algorithms of liver blood tests in liver fibrosis

In the UK, the National Institute for Health and Care Excellence stated, as part of its cirrhosis guidelines, that normal liver blood tests should not be used to exclude significant liver disease and recommended transient elastography to diagnose cirrhosis in people with known liver disease, in men regularly drinking more than 50 cL of alcohol per week and women drinking more than 35 cL of alcohol per week, and in people with chronic HCV infection.[278] These guidelines also recommended specific liver fibrosis markers in the form of the enhanced liver fibrosis test to stage fibrosis in people with NAFLD, and again cautioned against interpreting normal liver blood tests to exclude severe liver disease. However, the converse should also be highlighted: abnormal liver blood tests should not be disregarded.

The problem is that primary care and also many secondary care settings throughout Europe do not, in general, have access to a validated serum fibrosis test (eg, the enhanced liver fibrosis test), transient elastography, or other specialised fibrosis tests. They do, however, have access to routine liver blood tests, which allows for the application of fibrosis assessment algorithms with useful accuracy.[261,279] However, the wide range of liver fibrosis testing algorithms (appendix p 40), with varying expert opinions on which to choose, potentially undermines confidence and results in inertia and neglect by non-specialist clinicians. The *Lancet* Commission on liver disease in the UK made a recommendation for the ratio of aspartate aminotransferase to alanine aminotransferase, which has not perhaps stood the test of time and generally performs poorly in comparison to FIB4, APRI,[280] Forns index,[281] and CIRRUS[248] algorithms.

For clarity, this Commission has decided to recommend the FIB4 algorithm for European implementation at this point in time, while accepting that other algorithms, including APRI, Forns index, and CIRRUS, are also accurate. FIB4 can be calculated with basic clinical and laboratory parameters (eg, age, aspartate aminotransferase, alanine aminotransferase, and platelet count; appendix p 41). Online calculators are readily and freely available,[282] and there are many examples of locally adopted referral pathways using FIB4.[283] It should be emphasised that some population-based cohort studies showed that the reliability of FIB4 for assessing significant liver fibrosis is far from perfect.[265] While fibrosis measurement tools and algorithms are thus still evolving, we should not delay in communicating a clear and coherent recommendation for how to proceed at this point in time.

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Challenges of putting primary care pathways into practice

We cannot assume that primary care can or will automatically take on a major responsibility for people with liver diseases; the transfer of this workload to primary care practitioners faces substantial barriers (panel 1; appendix p 42), given that primary care in many European countries report unmanageable, underfunded workloads with inadequate capacity and restricted access to secondary care support.[286] Challenges arise at every step, particularly regarding the financial justification for any initial investment in screening strategies. Scaled-up testing and case-finding have an impact across biochemistry, haematology, and radiology—over and above that of hepatology and gastroenterology—all of which might have separate funding allocations, geographical restrictions, and competing priorities of their own. Additionally, decision making mechanisms for adopting new tests and pathways or for adopting solutions in information technology (such as embedding the FIB4 algorithm within a primary care computer system) might be locally or regionally, rather than nationally, determined, creating further challenges to standardisation when many more decision making panels and committees need to be involved. Successful change and investment will require evidence of benefit, cost-benefit analyses, strong advocacy, and partnered working within integrated care systems. The role of primary care regarding liver health is, as yet, unclear and undefined, reflecting the absence of incentivisation and inconsistent access to testing and referral.[274] Without understanding and addressing simple but common barriers (appendix p 42), progress to engage primary care will stall.

Barriers extend to those commissioning and investing in new services and infrastructure too. The timescales for showing beneficial outcomes or cost-savings from liver disease prevention might be longer than the typical time span of a commissioning cycle, so that further investment might be hard to justify if an inappropriate requirement to show within-cycle cost-saving has been imposed. This process is further perversely hampered if budgets are held in separate silos for primary and secondary care: primary care commissioners will be disincentivised to commit primary care investment that generates more work in primary care with resulting benefits that are only evident in reduced secondary care workload. The issue of capacity becomes a self-fulfilling problem of successful initiatives. The waiting times for transient elastography through the Scarred Liver Project rapidly escalated from 6 weeks to many months as local GPs became familiar and confident in referring through the pathway.[263,274]

The need for an increased role of primary care in the early detection of cirrhosis in individuals who are otherwise asymptomatic has been underlined by research.[265] In a survey of Italian family doctors, the general understanding of NAFLD was low.[287] Furthermore, although management

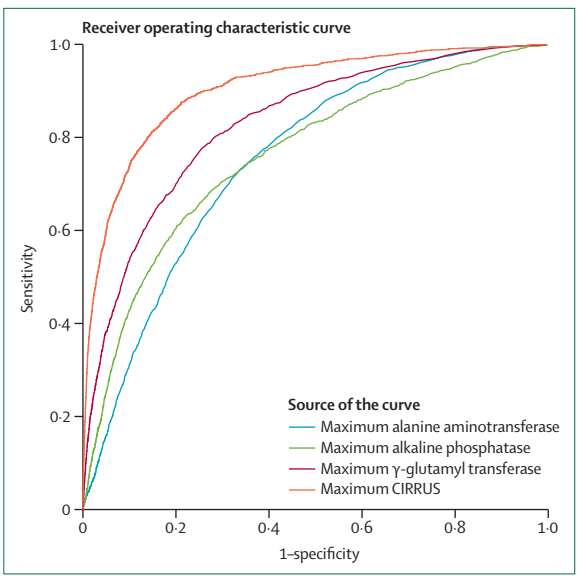

Figure 17: **Comparison of standard blood test results in patients in the CIRRUS dataset**

Of 394 253 individuals in the CIRRUS dataset[248] with a calculable CIRRUS result, 35 809 had data to allow comparison between standard blood tests for alanine aminotransferase, alkaline phosphatase, γ-glutamyl transferase, and one fibrosis algorithm (CIRRUS). Of these people, 1455 went on to have a first serious liver event (ie, admission with complications of cirrhosis, liver failure, or varices). AUCs were calculated for first, last, mean, and maximum blood test results. The maximum results had the highest AUC for prediction of a first subsequent serious liver event and are given here. Analysis by Nick Sheron. AUC=area under the curve.

of cirrhosis in primary care is critical and the majority of GPs see people with cirrhosis in their practice, only a minority assume responsibility for hepatocellular carcinoma surveillance and their knowledge of current complex modalities of treatment of hepatocellular carcinoma is understandably low. Screening for unhealthy alcohol use in primary care is infrequent and physicians who practise it are also those recognising that controlled drinking should be a key therapeutic goal.[288] Three overarching themes emerge in GPs' perceptions of their patients with cirrhosis: the complexity of comorbid medical, psychiatric, and substance issues; the importance of patient self-management; and challenges surrounding specialty care involvement and co-management of cirrhosis.[289] Although GPs feel they bring important skills to bear (care coordination in particular), they generally prefer to defer liver disease management to specialists.[288] There is a substantial opportunity to bridge this gap between primary and secondary care for people with liver diseases, but simplified and clear protocols and revenue streams to demarcate joined up care and maintenance treatment are required.

A number of gaps should thus be filled in the area of early detection of liver fibrosis in primary care, the most important being: (a) increasing awareness and understanding of liver diseases among primary care physicians and nurses, including their position within

multimorbidity management; (b) implementation of algorithms for early detection of liver fibrosis that could be easily applied to different primary care settings; and (c) improving interaction between primary care and hospital care for easy and rapid referral of individuals suspected to have liver fibrosis to be assessed in specialised settings.

The experience from hepatocellular carcinoma surveillance

All international guidelines recommend surveillance of high-risk populations for hepatocellular carcinoma with a view to early diagnosis, so that potentially curative therapy can be offered.[290] The population to be screened in Europe are those with cirrhosis, with ultrasound scanning as the method of surveillance. However, there are limitations of ultrasound surveillance, particularly in people with obesity—an increasing percentage of the European hepatocellular carcinoma population. A meta-analysis of 32 major surveillance studies involving more than 13 000 patients showed that the sensitivity of liver ultrasound was less than 50% for early hepatocellular carcinoma.[291] The addition of the biomarker α-fetoprotein slightly improved this figure to more than 60%. Inevitably, some of the benefit from hepatocellular carcinoma screening is related to lead-time bias but, where the impact of lead-time bias has been examined in detail, the benefit on survival from surveillance is still very substantial.[292,293]

In most European centres, hepatocellular carcinoma surveillance falls under the responsibility of secondary care. Although the adherence to hepatocellular carcinoma surveillance programmes in Europe in a published meta-analysis was 70%, higher than that in other regions of the world,[294] the true adherence is heterogeneous. The sheer load of patients with compensated cirrhosis undergoing regular ultrasonography can overload health-care systems (both the gastroenterology and hepatology departments and the radiology departments of hospitals, as well as outpatient specialist clinics). For this Commission, we analysed an international cohort of 5901 patients, including 2599 from Japan, 2190 from

***Panel 1*: Experiences in developing regional or national initiatives to improve diagnostic pathways of NAFLD and other chronic liver diseases in European countries**

Spain

In Catalonia, the northeastern part of Spain, a working group was created 3 years ago by the Catalan Society of Digestive Diseases to establish the best way for the diagnosis and referral of individuals with chronic liver diseases, such as non-alcohol-related fatty liver disease (NAFLD). This working group comprises members from the Primary Care Physicians Society, the Endocrinologist Society, and the Digestive Society. A consensus document[284] provided specific recommendations on which individuals should be screened, how this screening could be done in primary care settings, and which subjects should be referred to the secondary or tertiary health system for specialist review. In summary, this document recommended an algorithm for general practitioners that used non-invasive scores of advanced liver fibrosis (ie, FIB4 and NAFLD fibrosis scores) to rule out liver fibrosis in patients with risk factors for NAFLD.

Finland

A national guideline for NAFLD was published in Finland in January, 2020.[285] Production was a long, formal process, with translation issues adding to the complexity of achieving consensus. The International Classification of Diseases version 10 (ICD-10) was being used in Finland, which has cirrhosis related to non-alcohol steatohepatitis (NASH) but not NAFLD as a diagnosis. This discrepancy has been addressed in ICD-11 but it will take several years for newer nomenclature to be included in an updated translation.

UK

The Scarred Liver Project in Nottingham introduced an algorithm-based pathway for primary care doctors, involving risk factor-based case-finding and community transient elastography to detect cirrhosis. An initial barrier was the requirement to show short-term financial savings, although negotiations now have focused on longer-term horizons in chronic liver disease—both in terms of financial savings and lives saved. In September, 2016, a community pathway for liver disease in Nottingham was formally commissioned, covering a population of about 0·7 million, allowing primary care doctors to directly access diagnostic tests for liver fibrosis based on risk factors. Since 2016, about 5000 individuals have been stratified for liver disease; approximately 25% of these have significant liver disease, of which 40% would have been missed by national guidelines.

Greece

A collaborative project entitled Developing, Implementing and Evaluating a Clinical Care Pathway for NAFLD/NASH in Primary Care has been initiated in Crete, Greece. The overall aim of this project is to develop and evaluate an integrated, multidisciplinary, patient-centred model of care for NAFLD and NASH screening, diagnosis, and linkage to specialty care; and translate insights into a harmonised practice guideline for primary care. The model will combine the latest evidence-based practices and risk communication strategies. The project will provide primary care professionals with a state-of-the-art training programme and easily implementable approaches for establishing patient care pathways and integrated actions between primary care professionals and specialists. All project activities will be tailored by local experts and implemented in diverse settings in Crete (Greece), Barcelona (Spain), and Maastricht (Netherlands).

For more on the **collaborative project on the clinical care pathway in Crete** see http://www.nash.med.uoc.gr

Europe, and 1112 from China (figure 18). Although Japan has a formal surveillance programme, surveillance is only done ad hoc in Spain and the UK on the basis of individual physicians' recommendations, and no surveillance at all occurs in China. This gradient of surveillance intensity was reflected in patient outcomes: median overall survival was 47·2 months in Japan, 22·3 months in Europe, and 7·2 months in China. The proportion of patients accessing potentially curative therapies, such as resection, transplantation, or percutaneous ablation, was 71% in Japan, 35% in Europe, and 16% in China (figure 18).

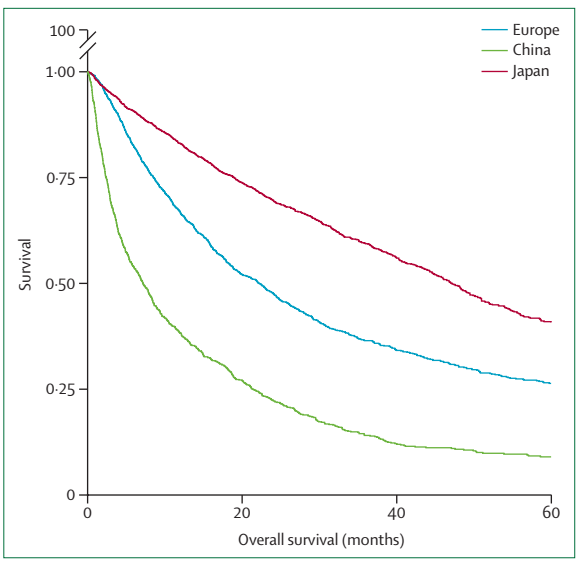

Figure 18: **Survival rates of series of patients from areas with different implementation of hepatocellular carcinoma screening activities**
The figure shows the effect of screening on survival rates. High: Ogaki (Japan); intermediate: Birmingham, Newcastle, and Pamplona (Europe); low: Hong Kong (China; appendix p 19).

A call for action to improve liver health in Europe

The state of liver health in Europe is taking a turn for the worse. Increasing pressures from sociodemographic factors and unhealthy behaviours are amplified by health systems, and the early diagnosis of preventable and treatable liver disease is hampered by shortcomings in effective case-finding mechanisms, barriers associated with the stigma of liver diseases, social inequities, and a general lack of attention and political will. Unless appropriate action is taken, negative trends already apparent in some countries with an increasing prevalence of liver disease (eg, the UK, Finland, and Bulgaria) might extend throughout Europe. The close relationship between risk factors for liver disease, social inequalities, and general health means that these developments are likely to reflect general health trends of our European population far into the 21st century. The strong link with health-related behaviours also represents an opportunity: there is a great potential to prevent liver disease from developing, especially if at-risk groups are identified early and effectively targeted for intervention.

Necessary actions will impact substantially on the way we organise health policies, health services, and the language we use when we converse about patients from marginalised segments of our heterogeneous and changing European population. How successful we are in bringing about changes for people with liver diseases will reflect how successful we are in advancing European health in general. A successful health policy will include a response to commercial forces working through rapidly evolving digital media and a shift in health systems from emphasising complications of end-stage liver disease to emphasising early diagnosis and management, especially in children who will soon be growing into the European working population in whom liver diseases currently make the biggest impact. As the COVID-19 pandemic has posed a stress-test to our health systems throughout 2020 and 2021, liver diseases will continue to serve as a sentinel for our capacity to deal with European health challenges over the next two to three decades. We should pay careful attention to this canary in the coalmine.

The EASL-*Lancet* Liver Commission has used the data in this report to lay out a long-term vision for liver health in Europe (figure 19; table 2), with several key actionable recommendations outlining how to move forward using these vision-oriented directions. The set of recommendations was selected by the Commission due to their potential to reduce not only the burden of liver disease in Europe, but also the proportion of this burden that is attributable to social inequities. Each recommendation is matched with a set of potential barriers and corresponding example actions for implementation. Although the first five recommendations mainly target health-care staff, community members, and patients, and the last five are mainly conceived for policy makers, most recommendations require multilevel interventions and are thus not stratified according to target audience. Many of our recommendations require deep national and international health policy changes to overcome the current factors that are fuelling liver diseases in Europe. In the remainder of this section, we will discuss how to proceed and the obstacles we will need to overcome on the basis of details given in table 2.

Focusing on early disease detection and primary care to bring about transformative change

Case-finding, health promotion, and long-term management are core roles for primary care,[295] the effectiveness of which can be enhanced by the involvement of specialised nurses and community members. There is considerable overlap between behavioural support and disease monitoring relevant to people with liver disease and other metabolic conditions. Transformative change is challenging not only due to the diverse multidisciplinary workforce that potentially affects liver outcomes, but also by a wide

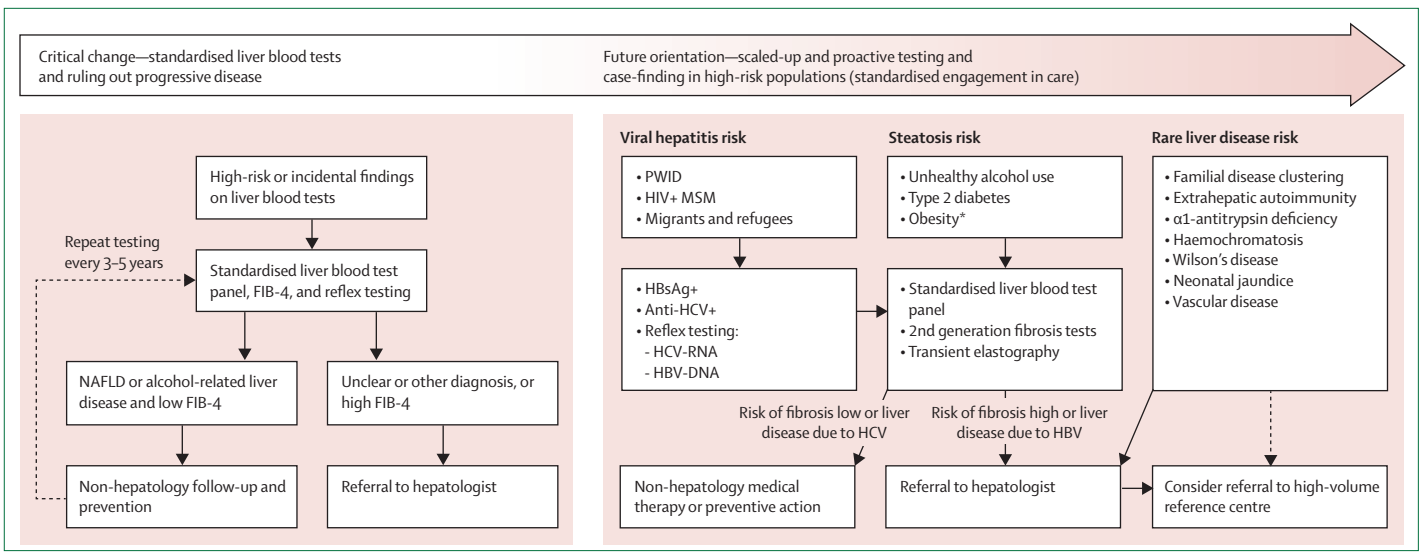

Figure 19: **A template for stratification of individuals at risk of liver disease for non-hepatologists**
The future orientation is towards case-finding and screening in high-risk individuals as indicated by the left and right panels, with the key distinguishing feature between primary and secondary care being the presence or absence of progressive liver fibrosis, not liver blood test abnormalities. This fibrosis-oriented framework should form the basis of a new interface between hepatology and collaborating specialties. Printed with permission from Kari Toverud. NAFLD=non-alcohol fatty liver disease. HCV=hepatitis C virus infection. HBV=hepatitis B virus. PWID=people who inject drugs. MSM=men who have sex with men. *For obesity, general screening cannot be recommended based on current evidence, and a key emphasis should be put on generating evidence to assess the cost-effectiveness of case-finding in this population.

array of health delivery systems and reimbursement mechanisms across Europe. Although educational steps to increase awareness and prioritisation of liver health will ultimately support improved care, in order for exemplary practice to become a feasible reality, change should first be facilitated by addressing many of the underlying drivers of health-care delivery, such as the standardisation of the liver blood test panel (appendix p 41), awareness and access to fibrosis algorithms (appendix p 40), and the development of models of multimorbidity care that incorporate liver health review alongside review of the so-called metabolic basket of shared comorbidities that are already commonly treated in primary care.[296]

For **more information on models of multimorbidity care** see https://www.yearofcare.co.uk/

Initiatives to promote standardisation of testing and care across Europe, including new digital health solutions, would help with economic arguments in countries where reimbursement mechanisms are a limiting factor in liver testing.[297] It is important to note that economic cost–benefit analysis is another challenging area when considering the patient with multimorbid-associated liver disease risk for whom the burden of care becomes increasingly relevant but features little in economic modelling, despite studies showing improvements in the people's lived experience of disease.[298]

Liver diseases related to unhealthy alcohol use and obesity are potentially preventable if the process of progressive fibrosis is detected and effective intervention to arrest progression is applied. There are potential economies of conversation, in which the same behavioural advice and multidisciplinary management applies across several disease areas, generating further economies of shared testing, care review, and delivery of behavioural interventions. Liver disease prevention should be included in these conversations, as part of a focus on multimorbidity and integrated, person-centred care,[296,298] rather than on medical specialty boundaries.

Overcoming barriers to primary care involvement in liver diseases

Enhanced primary care and specialist nurse engagement with simple care pathways focused on the detection and staging of progressive liver fibrosis will potentially pick up more patients in time to intervene, reduce worry and inconvenience from unnecessary referrals, and lead to efficiency savings from improved quality of referrals to secondary care.[299,300] Involvement of peers or community members can be a viable solution for reaching and self-empowering people with liver disease and ensure adequate linkage to care.[301,302]

Cardiovascular disease is generally well managed in primary care and supported by well evidenced care pathways and extensive secondary care resources. Consequently, mortality rates are decreasing throughout Europe (figure 2). The picture for liver diseases could not be more different, however, and much of the responsibility resides with the specialism of hepatology in providing similarly coherent guidance. The prevalence of liver disease is variable and can be highly concentrated, with dense foci of unhealthy alcohol and injection drug use.[303] Elsewhere, liver diseases form a smaller proportion of a primary care workload, with large variability between different countries in Europe. Thus, a nuanced but

mutually beneficial approach is needed; primary care health professionals with competing workloads could usefully recognise that focusing on liver disease and its interwoven relationship with other common metabolic comorbidities, such as obesity and type 2 diabetes, is relevant, feasible, and worthwhile,[304] while hepatology could help in communicating streamlined diagnostic and management algorithms. Although liver blood tests are widely carried out in relation to comorbidity monitoring, confidence in managing incidental findings is low, with evidence of ad hoc repeat testing (rather than appropriate further investigation) of minor abnormalities being the norm.[305]

We propose to focus on identifying people on the common pathway of progressive liver fibrosis, which will require a more balanced approach than the current, almost exclusive, focus on abnormal liver blood tests, which should be abandoned. Some people with elevated liver blood tests do have clinically significant liver disease but, for most people with mild elevations in liver blood tests and people at risk, the fundamental change needed is to focus early assessments on an evaluation of liver fibrosis. This Commission thus pragmatically recommends screening using first the FIB4 score followed by transient elastography or validated serum fibrosis tests intrinsic to liver disease testing (figure 19). In areas in which these new pragmatic care pathways have been introduced, such as the Scarred Liver Project, the experience has been positive for patients and clinicians, with projected longer-term health and economic benefits.

Importantly, these apparently simple solutions will require considerable system change, including investments in laboratory tests or elastography (ultrasound-based and magnetic resonance-based), with automated and digital response systems, in addition to actions by the individual primary care worker. We call for international consensus on these systems by professional medical associations and the establishment of multidisciplinary working groups to push for change across these organisations and coordinate advocacy directed at policy and health service funders. Agreement over the structure of revised services will then open up a

	Key barriers to implementation	Suggested actions for implementing recommendations
1. We recommend a simplified outreach approach (figure 18) using standardised liver blood tests with laboratory reflex-testing to facilitate early case-finding among individuals at high risk of liver disease, along with a consistent emphasis on fibrosis testing using FIB4 to rule out patients with advanced fibrosis; social inequalities are intimately linked to susceptibility to liver disease, meaning dedicated strategies are needed to engage disadvantaged groups in care	(A) Difficulties communicating about risk factors (eg, alcohol use) of liver disease; (B) Absence of coherent and simple algorithm recommendations to detect liver fibrosis for use outside of specialised settings; (C) Low health literacy of liver disease in the general population and in particular in disadvantaged groups; (D) Most severe cases are often difficult-to-reach individuals in marginalised communities; (E) Scarcity of health-care funding and or reimbursement	(1) Promote awareness of simplified algorithms for liver disease screening for health staff, in particular primary care physicians, to improve communication with patients and facilitate early detection of liver disease in high-risk groups (A); (2) Ensure laboratory implementation of computerised, automated algorithms of hepatic fibrosis markers for use during routine and specialist consultations coupled with appropriate reimbursement (B, E); (3) Support advertising and education programmes to increase health literacy in disadvantaged groups (C); (4) Use population-specific outreach approaches led by trained peers to better engage socially deprived groups in screening and care of liver disease and cirrhosis complications (D,E); (5) Prioritise management of more advanced or complex cases by specialists in the hospital setting, leaving that of less severe cases to primary care, specialised nurses, and community health settings (D, E)
2. We recommend investment to scale up case-finding and screening for viral hepatitis in selected (eg, primary care serving immigrants, harm reduction or drug services, and prisons) and broader community settings (eg, coupled with SARS-CoV-2-antibody testing), with reflex testing for viraemia for those with antibodies	(A) National plans only recommend testing in high-risk populations; (B) Insufficient financial support for nucleic acid testing (viraemia); (C) Failure to procure reflex testing for HCV RNA, HBV DNA, and anti-HDV in patients with a positive anti-HCV or HBsAg test; (D) Screening mainly done in secondary and tertiary health-care centres; (E) Programmes to control COVID-19 with emergent variants are challenging in disadvantaged and marginalised communities	(1) Support at national and local level for widespread testing for HBV and HCV based on past or present risk, and country of origin (A, B, C); (2) Updating laboratory protocols to automatically do HCV RNA and HBV DNA testing upon a positive anti-HCV or HBsAg test coupled with appropriate reimbursement (C); (3) Involve primary care and community-based practitioners, including GPs, pharmacists, addiction specialists, and prison services in the diagnosis and monitoring of liver disease and diagnosis of viral hepatitis (D); (4) Increase access to harm reduction for PWID, combining packages of OAT and NSPs, ensuring one or more sterile syringes for each injection to prevent acquisition (D); (5) Linking sentinel anti-SARS-CoV-2 serological testing to HBsAg, anti-HCV, and anti-HIV testing will increase the detection of hepatitis cases among disadvantaged communities (E)
3. We recommend that EASL and other medical specialist organisations collaborate to develop a European-wide syllabus for primary care hepatology with an emphasis on simplified patient-centred pathways and multimorbidity models of care, accounting for the collaboration between hepatologists and primary care clinicians, nurses, peer educators, and other medical specialties	(A) Absence of clear recommendations on what to do and systems and tools to do it; (B) Scarcity of time and incentivisation, including appropriate reimbursement; (C) Difficulties with managing behavioural disorders such as unhealthy alcohol use	(1) Facilitating simplified guidance on standardised scale-up of simplified testing and treatment (where appropriate) in primary care and other relevant specialist (eg, endocrinology) and community (eg, pharmacies, harm reduction or drug services, and prisons) settings (A, B); (2) Establish clear recommendations on the co-management of patients with liver disease by GPs, specialists, and specialised nurses; these recommendations need to be adapted to local contexts and resources (A); (3) Promote research to develop technology for detecting conjugated bilirubin (>25 µmol/L) in dry blood spots for detection of neonatal jaundice in primary care (A); (4) Promote incentivised involvement of primary care physicians, specialist nurses, and peer educators who together have a key role for lifestyle and risk factors modification, viral hepatitis elimination, detection of cirrhosis and comorbidities, and palliative care in advanced disease (B); (5) Promote the development of specialised nursing programmes for caring for patients with cirrhosis and engagement of individuals at high risk with testing (C)

(Table 2 continues on next page)

	Key barriers to implementation	Suggested actions for implementing recommendations
(Continued from previous page)		
4. We recommend that all non-viral liver diseases be classed as NCDs to allow the commonalities of NCDs to prompt a network of chronic care models, which include specialists, primary care physicians, and nurses, trained in obesity, diabetes, liver disease, cardiovascular disease, and chronic kidney disease, as well as peers and members of the community, to facilitate engagement in liver patient care across classical medical specialty boundaries	(A) Difficulty to set up chronic care models in disadvantaged areas; (B) Reluctance to abandon silo disease working by medical specialists and absence of appropriate reimbursement mechanisms; (C) Low public, parental, and professional awareness of paediatric liver disease and the importance of early diagnosis; (D) Scarcity of experience in handling rare liver diseases; (E) Difficulties in transition of care from childhood to adulthood; (F) Ageism (ie, stigma against people with age-related comorbidities), which affects health outcomes	(1) Promote alternative and low-cost models of care using health houses, primary care networks, pharmacists, specialist nurses, or community health sites (A, B); (2) Advocate for legislation regarding rights and protections for specific groups (eg, immigrants and children) of people (A, C); (3) Advocate for organisational policies in hospitals that oppose silo working by medical specialists (B, C); (4) Establish reimbursement mechanisms to account for patient-centric, multimorbidity models of care across a range of medical specialties (B); (5) Establish screening programmes for neonatal liver disease, routine genetic screening for inherited liver disease by gene panels, and standardised diagnostic and treatment protocols for paediatric liver disease (C); (6) Encourage centralisation of medical and surgical care for rare liver disease (C, D); (7) Identify a share-care model including adult and paediatric care providers, psychology and social services, and education to improve outcomes and empower the young patients to self-manage their condition in adult care (E); (8) Implement education and social contact interventions for chronic care model staff to fight against ageism (F)
5. We recommend a range of initiatives to oppose all forms and sources of stigma and discrimination of people at risk of or with liver disease using multilevel interventions that also involve peers and members of the community	(A) Self-stigma (internalised stigma) leading to care avoidance and delay; (B) Self-stigma resulting in unhealthy behaviours; (C) Persistent stereotypes resulting in discriminating attitudes from health staff; (D) Obsolete use of previous stigmatising terminology in medical literature and ICD-10 and ICD-11 coding systems (eg, using alcoholic or fatty)	(1) Offer patient education programmes involving peers for empowering, reducing self-stigma, and support engagement in care in people with liver disease (A, B); (2) Adopt when possible gender-tailored approaches as women are more concerned by stigmatising attitudes (A, B); (3) Introduce evidence-based anti-stigma training programmes for health staff based on social contact with community members who deliver their own experiences with discrimination and its effects (C); (4) Change WHO ICD-12 liver disease coding to reflect an updated nomenclature on liver disease, with removal of stigmatising terms, such as alcoholic, and more rational coding for all forms of non-viral hepatitis and obesity-related liver disease; during clinician–patient encounters, the name of the disease should reflect the clinical disease as opposed to outdated behavioural or histopathological terminologies (D)
6. We recommend public disclosure of pricing information of approved antiviral drugs currently used to treat viral hepatitis in Europe, which would reinforce the WHO and World Health Assembly resolution to improve the transparency and fairness of market prices for medicines	(A) Absence of uniform systems of state health coverage, and variability in reimbursement systems and health insurance for treatment of viral hepatitis across Europe; (B) Restriction of antiviral therapy to hospital specialists, due in part to the high prices of antiviral therapy in some countries; (C) Scarcity of access to generics in most European countries; (D) Absence of primary care prescription of HCV treatment	(1) Set up an observatory to ensure transparent pricing of antiviral drugs in the WHO European region (A, B, C); (2) Implement a monitoring system for access to antiviral drugs in the European regions to reduce gaps in specific areas or groups and simplify treatment pathways (A); (3) Provide guidelines stating unrestricted access to antiviral therapy (including generics) in Europe for HCV irrespective of fibrosis stage (B, D); (4) Establish mechanisms for prescription of HCV therapy in primary care and community services coupled with appropriate reimbursement (B, C, D)
7. We recommend that European governments introduce uniform and effective policies to reduce the harmful use of alcohol; specifically, we recommend that a minimum price of €1/cL of pure alcohol (MPC) is introduced across all countries of the EU and associated countries and that the MPC is accompanied by appropriate increases in alcohol taxation to ensure that any MPC windfall to retailers is returned to government finances	(A) The stigma related to unhealthy alcohol use from all sections of society, including policymakers and hepatologists; (B) Failure of the medical profession to make effective evidence-based arguments for alcohol policy as were made successfully for tobacco; (C) Limited power of communities and patients to lobby for change, related to the stigmatisation of people with unhealthy alcohol use; (D) Strong, coordinated opposition from the alcohol industries; (E) Absence of standardised high-quality data to monitor effects of policy changes	(1) Ensure WHO Europe (EU and non-EU European countries) coordination to monitor implementation of alcohol policies (B, D); (2) Verify taxation funds are used to promote health community services and social insertion for people at risk of unhealthy alcohol use (B, D); (3) Implement attractive care strategies for people with unhealthy alcohol use that aim for controlled drinking and harm reduction as outcomes (A, B, C); (4) Promote effective advocacy campaigns led by the medical professions and the community to change alcohol policies (A, B); (5) Ensure support from the European Court of Justice and UK Supreme Court to defeat challenges from industry (D); (6) Ensure availability and access to high-quality standardised data to provide accurate estimates of the burden of liver disease complications and the impact of population-level policy interventions, similar to the monitoring of diagnosis and mortality of COVID-19 in real time (E)
8. Recognising the deleterious impact of the marketing of alcohol and ultra-processed, high-sugar food and drinks to children, we call for attention to unregulated narrowcasting of marketing messages to mobile phones by digital and social media; experience from the tobacco industry has shown that the only effective means to protect children is through a complete ban on the marketing of alcohol and HFSS foods, and hence we call for such a complete ban in all social and digital media	(A) Industry lobbies; (B) Low understanding of the business models of social media marketing; (C) Global sites and social media commonly visited by children that expose them to large amounts of alcohol or HFSS marketing; (D) National government difficulties in regulating multinational corporations in the advertising area related to children health	(1) Delegate to the EU and WHO Europe the leadership to make countries apply uniform marketing regulations in all social and digital media, expanding from the AVMSD and the CLICK campaign (A); (2) Promote in-depth analysis to identify better responses to contrast the effects of marketing business models of social media (B, C, D); (3) Promote multicomponent school-based interventions focusing on both physical activity and healthy diet in children with obesity (C); (4) Adopt models that better identify when marketing strategies indirectly or directly target children—eg, model used by the US Federal Trade Commission COPPA (C, D)

(Table 2 continues on next page)

	Key barriers to implementation	Suggested actions for implementing recommendations
(Continued from previous page)		
9. We call for policy measures to promote industry-led food reformulation and the minimisation of social inequities by subsidising healthy foods	(A) Availability and access to ultra-processed foods, HFSS, cigarettes, and drugs higher in disadvantaged areas; (B) Cultural barriers (eg, family or community habits and lifestyles); (C) Economic barriers (eg, affordability of healthy food)	(1) Disseminate prevention spots, and facilitate availability of low-cost healthy foods, harm-reduction services, and educational programmes (A); (2) Promote food labelling—eg, nutriscore and removal of cartoons and other children-oriented branding (B); (3) Involve communities to increase food literacy (B); (4) Apply HFSS-related taxation and use taxation funds to: involve members of the community in prevention and increase job opportunities in disadvantaged groups; subsidise prevention, from healthy food to physical activity programmes and anti-stigma interventions; create low-threshold sites for obesity prevention to be used as entry points and referral to care in disadvantaged areas (C)
10. We call for a coordinated and systematic public health case to be made to rebut the nanny-state and pseudoprotective arguments, which favour exclusion of specific groups and obstruct population-level policies to reduce liver disease mortality; in particular, the EU and European governments should prioritise the harmonisation of all forms of public health interventions across Europe with a particular emphasis on vulnerable groups, such as children, people who inject drugs, immigrants, and the less affluent	(A) High cost and economic losses; (B) Environmental effects (eg, marketing) counterbalancing prevention efforts; (C) Cultural and political heterogeneity of Europe	(1) Use taxation to subsidise health services and increase access to healthy food (A); (2) Implement a monitoring system for inequalities in access to specialised care for patients with cirrhosis (A); (3) Adjust health information to various populations (culturally adjusted, in several languages, and with lay explanations) and explore ways to effectively disseminate it (B); (4) Create uniform legislation in European countries to restrict advertising and aggressive marketing, especially among less affluent populations and children (B, C); (5) Establish mechanisms for rewarding voluntary industry initiatives (responsible industry actions) for healthy food reformulation (B); (6) Convince policy makers and the public that food and drink intake is not really a matter of free choice, but rather heavily influenced by the actions of the food industry (so-called nanny industry), driven by economic interests (B, C)

The panel of recommendations was developed by a Delphi-like consensus process among the Commissioners, through a series of physical and digital meetings. For each of the ten recommendations, we have listed key barriers to their implementation and example activities to facilitate actual change. The list of example activities is not exhaustive, and priorities and actual implementation will be important tasks during further work of relevant stakeholders. AVMSD=Audiovisual Media Services Directive. COPPA=Children's Online Privacy Protection Act. GP=general practitioner. HBV=hepatitis B virus. HCV=hepatitis C virus. HDV=hepatitis D virus. HFSS=high-fat, high-salt, high-sugar food. ICD=International Classification of Diseases. MPC=minimum price of €1/cL of pure alcohol. NCD=non-communicable disease. NSP=needle and syringe programmes. OAT=opioid agonist therapy. PWID=people who inject drugs.

***Table 2*: Recommendations of the EASL–*Lancet* Commission on liver disease in Europe**

route to developing an, as yet absent, international framework for education in liver disease tailored to primary care, starting in Europe.

Models of care in established liver disease: accounting for multimorbidity

A common barrier to optimal care is a delivery system that is often fragmented, lacks clinical informatics capabilities, duplicates services, holds an emphasis on traditional medical specialty boundaries rather than patient needs, and is poorly designed for the coordinated delivery of chronic care in people with multiple comorbidities. From the physician's perspective, integrated care for people with multiple morbidities and chronic diseases warrants multidisciplinary approaches, and bridging of traditional boundaries between medical specialties. From the patient perspective, multimorbidity models of care serve the same purpose and might lead to better integration and improved coordination of services. The widely recognised chronic care model is a patient-centred, evidence-based, proactive framework[8] that has been adopted and implemented for many NCDs, including type 2 diabetes, hypertension, and cardiovascular disease,[306–308] and which applies to both of these perspectives.

The Sustainable Development Goal (SDG) target 3.4 is to reduce premature mortality from NCDs by a third by 2030 relative to 2015 levels.[309] Reducing liver-related mortality has the potential to make a major contribution to achieving this goal, but it faces a number of fundamental barriers. The first barrier is the widespread perception that liver diseases do not belong to the domain of NCDs. This is a flawed perspective probably resulting from the past focus on the global burden of viral hepatitis rather than that of the growing non-communicable forms of liver diseases, such as NAFLD or those resulting from alcohol and various autoimmune and vascular causes that predominate in Europe and to which more than 80% of European liver transplants are attributable (figure 20). The second barrier is that cirrhosis is listed among non-NCD causes of death, in contrast to cardiovascular diseases, chronic respiratory diseases, and diabetes. However, there is a large body of evidence on the burden of end-stage liver disease due to NAFLD in people with NCDs, particularly in high-risk groups such as people with obesity and type 2 diabetes. It is notable that neither the *Lancet* Commission on type 2 diabetes,[310] nor a large review of overweight in 195 countries mention liver-related complications, including NAFLD, cirrhosis, or hepatocellular carcinoma.[311] This misperception should be changed and underscores the urgency to modernising liver disease pathways and investment in holistic services to avoid overlooking the risk of cirrhosis and hepatocellular carcinoma in people with metabolic syndrome, obesity, and type 2 diabetes. Liver-related morbidity is one of the possible outcomes in a wider risk scenario, as exemplified by NAFLD, obesity, and type 2 diabetes.[306,307]

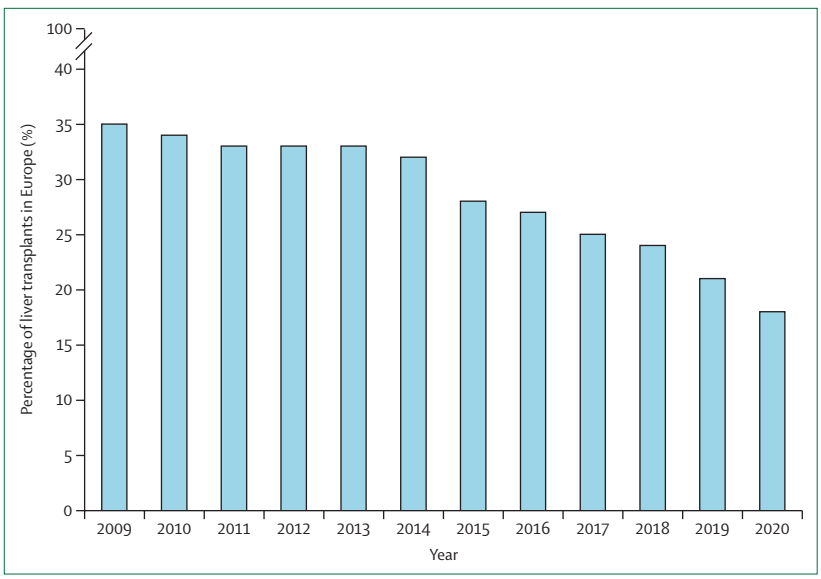

Figure 20: **European liver transplants attributable to viral causes**
Data plotted with permission from the European Liver Transplant Registry.

Non-communicable liver diseases and the chronic care model

The chronic care model addresses six aspects of care delivery: organisational support, community-linking, self-management support, decision support, delivery systems design, and clinical information systems.[8,306] In the field of liver diseases, there is some experience from the model in late-stage liver disease—eg, for the long-term management of cirrhosis as the end-stage NCD of all liver disease aetiologies—to increase integration with multidisciplinary services in primary care, district hospital liver units, and specialist centres.[12] In a study in Italy, use of a structured chronic care model for patients discharged from hospital with ascites showed it significantly reduced 30-day readmissions (from 42% to 15%), 12-month readmissions (from 71% to 46%), and 12-month mortality (from 46% to 23%) while achieving a 46% reduction in health-care costs.[312] We propose that an adapted chronic care model is applied at the early stages of liver disease, as part of a proactive practice starting from primary care that promotes education and the empowerment of individuals at risk of NCDs, with selective referral to hospital for further diagnosis and treatment only for severe, complex, or rare cases.

In many cases, lethal outcomes from COVID-19 have occurred on a substrate of NCDs, many of them shared with and fostered by NAFLD. Nevertheless, NAFLD is barely mentioned in international and national guidelines on NCDs and is missing in the WHO webpage on obesity complications. Complex diseases and multiple needs of individuals with metabolically driven NCDs require stratification of the competing and often co-occurring risks (eg, cardiovascular disease, diabetes, chronic kidney disease, and liver disease) that need to be addressed.[71] This stratification allows the delivery of integrated interdisciplinary management with ongoing support to individuals with multiple comorbidities, liver disease included, and their associated complex needs. That the pathological processes of metabolic liver disease are intertwined with COVID-19 severity underscores the need to modernise liver disease pathways and increase investment in holistic services that include liver disease perspectives.[313]

Many chronic care model programmes already exist across a spectrum of different NCDs, both at the level of general hospitals and specialist centres. To maximise efficacy, these programmes should be integrated in a wider, comprehensive chronic care model that includes primary care and a liver perspective. Effective and durable achievements are not feasible if addressing only a single disease or cause of morbidity and mortality. It is time to include liver diseases within the spectrum of NCDs related to metabolic disorders by creating platforms for collaborative work (including non-communicable liver diseases), which will enhance the collective efforts of multiple actors across diverse medical specialties and sectors of research and health care, with the patient at the centre of their own care needs.

Merging chronic care models that include liver diseases into integrated and data-driven multimorbidity care also gives the opportunity to create a synergy of research and action. Systematic data collection in chronic care models can help to establish a multidisciplinary register for providing the information required to stratify risk, identify needs, personalise care, and treat multiple targets. Unified data management systems can support research based on this type of 360-degree knowledge of the patient and transform the care of NCDs. Several of the needs require simple technological solutions, such as reflex testing rather than repeat testing. The effective reshaping of existing chronic care models to provide integrated care requires, on one hand, the engagement of nurses and non-medical personnel with relevant knowledge and skills and, on the other, the use of technology to improve accessibility and interactions.

Nurse-led care for people with established liver disease

Specialist liver nurses could play an integral part in case-finding and the care of people with liver disease, and bridge gaps between clinicians and patients and between primary and hospital care. They also could have an important role, both in community and hospital settings, in providing health education to patients and families and stimulating the engagement of patients in their own care, aspects that are barely present in the current care for people with liver disease. Benchmarked standards for different roles in nursing will need to be developed for skills, knowledge, and competencies. To our knowledge, the UK Royal College of Nursing guidance *Caring for People with Liver Disease: a Competence Framework for Nursing* is the only available document in Europe that

For the **WHO webpage for obesity complications** see https://www.who.int/health-topics/obesity#tab=tab_1

describes the professional standards for nurses when caring for people with liver disease.[314] In this model, the key role of nurses would be to actively coordinate and promote liver services across the appropriate care pathway. Embedding more knowledge of liver diseases throughout the training of nurses and doctors will improve consideration of liver care by the wider health-care team when caring for people with associated comorbid conditions.

The role of specialist liver nurses in the care of people with cirrhosis has been proposed by the LiverHope nursing project, a task force of nurses from different European liver units with expertise in people with cirrhosis working in an EU-funded Horizon 2020 project.[315] The project has identified specific activities of nursing care for inpatients and outpatients with cirrhosis and their specific complications,[316] and should bring valuable model experience for the further implementation of nurse-led models for people with liver diseases in Europe.

The nurse-led model also holds relevance for the aforementioned gaps in paediatric and transition care. In the informal query among 62 paediatric centres from 25 countries in Europe mentioned previously, more than 80% had full diagnostic facilities, more than 70% had specialised multidisciplinary teams, and 48% provided liver transplantation. The main weaknesses were low levels of family support (51%) and organised transition services from paediatric to adult care (<60%). A global framework document is necessary at the European level and should include skills and competencies of specialist liver nurses both at the community and specialised settings and how they are best incorporated into care pathways. Methods of attaining competencies and skills will be country-specific and we, as Commissioners, strongly advise the use of our report as a starting point for reshaping the role of nurses in liver services across Europe.

Pathways of care in established and advanced liver disease

Cirrhosis should be considered a distinct, complex, and severe disease that represents the final stage for any aetiology within the spectrum of chronic liver diseases (figure 4). People with cirrhosis are sometimes diagnosed before the development of complications (compensated cirrhosis) but are unfortunately most commonly diagnosed after development of such complications (decompensated cirrhosis).[317,318] Although mortality due to cirrhosis has decreased during the past three decades in Europe,[319,320] the burden of decompensated cirrhosis has in fact increased. In addition, current indications for liver transplantation in cirrhosis are changing, with a steady rise in people with NAFLD and a considerable drop in those with HCV infection,[22] indicating a shift in the burden of specific causes of cirrhosis. The changing landscape of cirrhosis in Europe requires an urgent assessment and action plan to adapt the care of patients with cirrhosis to the changes in underlying causes.

Traditional care pathways for cirrhosis predominantly involve hospital-based care and provide marginal survival benefits at very high costs. Major disparities exist between countries in terms of access to care, models of co-management of people with cirrhosis, and integration of nurses. Currently, some countries almost exclusively delegate management of the disease to specialised units in hospitals while, in others, primary care has an integral, collaborative role. However, pathways linking primary and secondary care are ill defined and underdeveloped in many countries throughout Europe. The complexity of cirrhosis, with its various potentially severe complications and diverse causes, might be in part responsible for the difficulty in establishing good collaboration between primary and secondary care. This Commission strongly urges for a shift towards a flexible yet uniform model of task distribution on the management of cirrhosis between primary or secondary care (table 3).

GPs and nurses working in primary care can intervene in four fundamental areas: detection of cirrhosis; behaviour and risk factor modification; screening programmes in compensated cirrhosis; and palliative care in advanced disease.[321] The diagnosis of asymptomatic compensated cirrhosis in the primary care setting relies heavily on the recognition of risk factors and follow-up with appropriate investigations. The potential impact of primary care in the management of alcohol and metabolic risk factors might become important upon implementation of adequate training. The role of primary care in the co-management of people with cirrhosis, such as for hepatocellular carcinoma surveillance, requires further research. As technological

	Community-based hepatology or primary care	Hospital-based or specialised care
Patients with compensated cirrhosis	Management of causal factors in alcohol and metabolic-dysfunction-associated cirrhosis Curative treatment of hepatitis C Coordination of regular screening for hepatocellular carcinoma Coordination of regular screening for gastro-oesophageal varices Health education for patients and caregivers Management of comorbidities Identification of perceived stigma	Management of causal factors in hepatitis B-associated cirrhosis Treatment of hepatocellular carcinoma
Patients with decompensated cirrhosis	Child-Pugh grade A–B patients in stable condition (without recurrent complications and with steady treatment) Health education for patients and caregivers Management of comorbidities Patients under palliative care (regardless of Child-Pugh grade) Identification of perceived stigma	Unstable Child-Pugh grade B–C patients, with recurrent complications Patients with specific complications, such as refractory ascites, acute kidney injury, bacterial infections, and overt hepatic encephalopathy Curative treatment of hepatitis C Patients suspected of having alcohol hepatitis Treatment of hepatocellular carcinoma Patient candidates for liver transplantation Health education for patients and caregivers

Table 3: **Examples on sharing of responsibilities for the management of cirrhosis between primary care and specialised care**

advances increasingly allow electronic case-finding and intervention delivery for relevant liver disease risks, the importance of careful coding in the primary care record of both risk factors and established diagnostic terms cannot be overstated.[322] Among the multiple barriers to broadening the role of primary care (appendix p 42), the absence of clear and consistent guidance on how to choose among the spectrum of fibrosis algorithms proposed throughout the literature should be an easy fix (figure 19, appendix p 40). From the patient perspective, the absence of simplified guidance adds to the feeling of discrimination and the complexity of the health-care pathways as main barriers to engagement in liver disease care.[323] In one qualitative study, the presence of national guidelines, combined with clear flowcharts or computer prompts, increased the confidence of primary care workers in their diagnostic capabilities.[324]

The issue of end-of-life care in advanced liver disease is an area within which much can be improved. An international systematic review on the perspective of patients, their caregivers, and health-care professionals highlighted important issues in patients' limited understanding of the disease and in providers' difficulties in communicating information.[325] Primary care plays a fundamental part in end-of-life care,[326–328] yet also faces multiple challenges, including the complexity of symptom management, complex social circumstances, and lack of confidence in having discussions about prognosis and future care preference.[321,325]

By redefining roles of primary and secondary care in management of people with cirrhosis, the attention of hospital care can be paid to complex cases. Indeed, the subset of patients with cirrhosis who develop complications represents an important amount of the workload of the overall hospital care, both for the day hospital and the inpatient wards. This workload is related to the high prevalence of the disease, the variety of complications patients can develop, and the frequent recurrence of these complications, particularly hepatic encephalopathy, ascites, and bacterial infections. In a study from Catalonia in Spain, the overall cost associated with care of people with cirrhosis during a year represented 1·8% of the total annual budget of the health-care system; moreover, 35% of the costs were related to hospitalisations.[329] Reports from Germany, Portugal, Scotland, and Denmark confirmed a very high frequency of hospitalisations of people with cirrhosis and the same might be true for other European countries,[330–333] underscoring the relevance of the proposed task distribution.

For the **RARE-LIVER network** see https://rare-liver.eu/

Moreover, hospital readmissions are very common due to the recurrent nature of cirrhosis complications. In fact, cirrhosis has one of the highest rates of early readmissions among different medical conditions, including cancers.[334] Several factors associated with the risk of readmission have been reported, which makes it possible to identify people at high risk of such an outcome.[335,336] Several reports indicate that either the use of planned care for specific complications, such as large-volume paracentesis for refractory ascites, or a quality improvement programme based on electronic decision support reduce readmission rates in people with cirrhosis.[337,338] Increasing the collaboration between primary and hospital care might reduce the high rate of hospital admissions of people with cirrhosis and help improve quality of life for these patients.

The application of multidisciplinary approaches in specific areas

The treatment of liver cancer is complex and costly, interdisciplinary, and involves therapies that are rarely used for other tumours (eg, liver transplantation, percutaneous ablation, or intra-arterial therapies), while systemic therapy has a small but increasing role. As with other complex medical conditions, the ideal way of providing optimal therapy is through a multidisciplinary team. In practice, access to care in networks of multidisciplinary teams is difficult and inequalities are perceived by participating physicians (appendix p 43). The multidisciplinary team for liver cancer should involve at least the core involved specialties (hepatology, liver and transplant surgery, diagnostic and interventional radiology, medical oncology, and pathology) and discuss all patients irrespective of staging or liver function status. When liver transplant surgery or interventional radiology is not available in small centres, the participation of specialists from other hospitals should be secured, using, for instance, telemedicine participation or digital conferencing.

Despite a considerable part of the European population being affected by rare liver diseases, health-care systems in many European countries are not set up adequately to provide high-quality care.[339,340] Multidisciplinary services provided to many of these patients, such as those with primary sclerosing cholangitis and biliary atresia, and specialised surgical procedures in particular show enhanced quality of care associated with centralisation of care services that lead to elevated caseloads. Outcomes following the Kasai procedure in patients with biliary atresia are significantly better in centres performing a higher caseload (five or more cases per year) versus low-volume centres.[82,333,341,342] The EU has recognised the challenges and need for action and thus supported the implementation of a European Reference Network for rare liver diseases in both adults and children (RARE-LIVER).[80] However, at the time of implementation of the European Reference Network, only 50% of children with biliary atresia in the EU were being cared for in RARE-LIVER-certified centres. Furthermore, European countries that are not EU members are excluded from being full members of this programme. We believe the programme should be more inclusive across the whole of Europe, and that it holds an important model example for the harmonisation of health systems in Europe, far beyond the topic of rare diseases.[343]

Opportunities of telemedicine and new pathways of care

The changes to health-care delivery systems triggered and demanded by the COVID-19 pandemic provide a unique opportunity to improve liver disease care.[344] Change is now the norm and all clinical practices are being reviewed, adapted, and modernised, reflecting the necessity to streamline care and use technology to optimise outcomes. There has been a major shift towards remote working, using phone, text messages, and video-calls, and much wider triaging of patients before, or instead of, face-to-face assessment.[345]

The move to telemedicine has facilitated remote delivery of care, allowing increased access to care for those in isolated environments as well as those currently fearful of attending clinics. All these opportunities should be used to foster a digital framework of multidisciplinary care for liver diseases under the guidance of scientific societies. From a governmental standpoint, such a framework will require allocation of sufficient financial resources for integration of these models into existing digital health-care platforms and investment in artificial intelligence-driven remote health systems to integrate the entire continuum of care. At the interface between primary and secondary care, telemedicine has also reduced hospital outpatient appointments as secondary care assessment has shifted substantially to remote assessment, with increased use of advice and guidance mechanisms to respond to referrals (whereby consultants write back to GP requests for advice rather than taking over responsibility of the referral).[346] However, the stopgap use of telemedicine and its impact on health inequalities is yet to be evaluated as reduced face-to-face assessment is likely to have differential positive and negative effects across different groups.

Responding to stigma and discrimination

Reducing stigma and discrimination towards individuals at risk of liver diseases cannot be achieved without a combination of interventions targeting the multiple layers of stigma, in particular stigma in health-care settings, structural stigma, and self-stigma (figure 15).[347] Such multilevel anti-stigma interventions are needed to reduce delayed consultation and care avoidance, and ensure optimal and timely prevention and care of people concerned by liver disease. For children with obesity, multilevel interventions tackling societal and commercial determinants of obesity alongside addressing associated comorbidities, stigma, and social disparities,[170] while promoting comprehensive packages of health care and involvement of parent associations, have the potential to counteract the growing childhood obesity epidemic.[348]

At the health-care level, education and social contact interventions in the training of medical and nursing students should be implemented, as well as social contact interventions led by peers or community members to health-care staff. For all liver diseases, as stigma is an issue, health-care services should offer disclosure support to people unable to disclose their disease or behaviours. Particularly for HBV and HCV, testing guidelines should put forth how to increase testing and treatment in high-risk groups, such as sex workers, homeless people, men who have sex with men, PWID, and immigrant populations. Education about the strong genetic basis that underpins the risk of obesity might help to combat the entrenched misperceptions that obesity is in some way a personal choice or a failure of willpower, and to add legitimacy to medical and surgical obesity treatment recommendations.

To fight against self-stigma, there is a wide and increasing spectrum of multitargeting interventions, combining objectives of promoting self-esteem and self-efficacy, empowerment from the support of peers or the community, education to discard stereotypes, increased social and coping skills, and encouragement of treatment engagement.[349] Many of these interventions can be incorporated in treatment education programmes (eg, also including nutrition or harm-reduction strategies) and delivered by peers or health-care staff other than physicians.[350]

Health policy makers and clinicians must encourage stigmatised populations concerned by liver disease to get tested and identify innovative entry points for screening and treatment in settings beyond specialty care, such as primary care, prisons, and community sites. In a post-COVID-19 era of economic restraint, the involvement of peers or use of community services—eg, needle and syringe exchange services for PWID, parent associations for children with obesity, and immigrant community settings—can substantially reduce costs and create novel and trusted entry points for prevention and care. Peers and community members can provide education on prevention, facilitate case-finding, promote early diagnosis, fight against label avoidance, and act as navigators to ensure linkage to care,[351] thereby preventing dangerous delays or discontinuation of care, which disproportionately contribute to the current burden of liver disease in Europe.

It is the opinion of this Commission that the guiding principle should be that restrictions on access to liver care based on behaviours should be minimised or removed. Restrictions based on alcohol or drug use abstinence or weight reduction can be regarded as a type of structural stigma and discrimination that is likely to leave the most socially vulnerable behind and increase the burden of liver disease in the most socially deprived groups. For HCV and HBV, the introduction of point-of-care testing and oral antiviral drugs warrants appropriate care for all groups. Thus, removing all stigmatising barriers and obstacles to diagnosis and treatment, including the insistence on abstinence from substance or alcohol use, is obligatory. As elaborated further on, treatment restrictions must not be imposed. Treatment deferral should only be advised by providers when it is necessary to ensure the

safety of individuals. For alcohol and obesity, the case is more complex, as exemplified by liver transplantation. For alcohol-related liver disease, prolonged abstinence (3–6 months) is a key criterion for acceptance to the European liver transplant waiting lists. The notion that liver transplantation for patients who did not remain abstinent during the pre-transplant period does not appear to affect long-term survival despite the higher risk of relapse[352] has to be balanced against donor perceptions and local availability of management programmes for avoiding relapse to harmful alcohol use after transplantation. In the field of NAFLD or NASH, severe obesity is generally a contraindication for liver transplantation because of the high risk of complications in this group. Therefore, it becomes essential to reduce harms from both obesity and muscle wasting before and after transplantation through the delivery of comprehensive interventions combining specific nutritional approaches or exercise, or both.[353]

	ICD-11 code	Adjusted term(s)	Future considerations
Alcoholic liver disease	DB94	Alcohol-related liver disease; steatosis	Alcohol remains a key risk factor for liver disease and complete removal of alcohol from nomenclature removes the responsibility related to alcohol regulations
Alcoholic cirrhosis of the liver without hepatitis	DB94.3	Cirrhosis due to alcohol-related liver disease; cirrhosis	Synergy of multiple risk factors is prevalent; consider cirrhosis as a separate entity from risk factors with emphasis on complications
Alcoholic hepatitis	DB94.1	Alcohol-related acute liver injury; acute liver injury	Pathophysiological specification upon new knowledge
Primary biliary cholangitis	DB96.1	Primary biliary cholangitis (previously called primary biliary cirrhosis)	Aetiological classification upon new knowledge
Non-alcoholic fatty liver disease or NAFLD	DB92	Metabolic-associated fatty liver disease or metabolic dysfunction-associated fatty liver disease or MAFLD; steatosis	Pathophysiological specification; account for synergy of multiple risk factors
Non-alcoholic fatty liver disease without non-alcoholic steatohepatitis	DB92.0	Fatty liver disease; steatosis	Pathophysiological specification; category to account for synergy of multiple risk factors
Non-alcoholic steatohepatitis	DB92.1	Steatohepatitis	Pathophysiological specification; category to account for synergy of multiple risk factors; add consideration for fibrosis (missing for NAFLD in ICD-11)
Alcoholic, drinker	NA	Person with alcohol use disorder	NA
Drug addict, drug abuser, intravenous drug user, injecting drug user	NA	Person who injects drugs or person who uses drugs	NA
Someone receiving substitution treatment[5]	NA	A person in an opioid agonist therapy programme (not simply replacing or substituting one drug for another)	NA
Prostitute (prostitution)	NA	For adults (aged 18 years and older): sex work, sex worker (sex work, commercial sex, or sale of sexual services); for children (younger than 18 years): sexual exploitation of children	NA
Target populations	NA	Priority populations, key populations	NA

The WHO ICD-11 codes,[354] to be launched in 2022, are given above together with adjusted terms that reflect recommended terminology with patients and future considerations. The table reflects a move to focus on the name of the condition and not the cause of the condition. Risk factors overlap and attribution can be difficult or even mixed and often stigmatising, such as when using the terms alcohol or fat. The new nomenclature is intentionally simple, to be used during the clinician–patient encounter. ICD=International Classification of Diseases. NA=not applicable.

Table 4: **Revisions to reduce structural stigma resulting from aberrant liver disease nomenclature**

Concerning structural stigma, a key step is to change all stigmatising nomenclature, as we propose in this Commission (table 4).[354] Words matter. Names matter. Stigmatising terminology, even if used unintentionally, can have devastating consequences for those affected by such terms, including reduced health-care seeking behaviour. It is the strong opinion of this Commission that the entire liver health vocabulary requires a language revision to amend stigmatising terms, wherever they might be used (eg, in clinical guidelines, ICD codes, strategies, action plans, reports, and conference session titles). Therefore, in table 4, we have listed potentially stigmatising terms commonly used in the liver field and how they have been revised (eg, by EASL in its clinical practice guidelines) or might be revised moving forward.

However, in spite of an important revision in 2018 of terminology for alcohol-related liver disease,[238] none of the proposed terms have been implemented in the upcoming ICD-11, to be launched in 2022.[354] WHO needs to be made aware of the potential for their current and upcoming nomenclature to increase stigma. In line with the efforts of affected communities, we encourage the use of people-first language, which focuses on the person rather than their ailment or diagnosis, thus emphasising the dignity of the individual. As noted further on, describing someone as a PWID rather than an injecting drug user helps reduce the stigma associated with injecting drug use.

We do not claim that the revised terminology in table 4 will remove all structural stigma of liver disease nomenclature. The suggestions are intended to inform a deeper, global conversation that medical associations, patient groups, and representatives of affected communities need to initiate in the coming years to address and agree on new destigmatising language. National language differences throughout Europe will need to be accounted for, and we hope that our proposals might serve as a blueprint for the desirable direction of travel for these activities. A complete removal of potentially stigmatising terms, such as fat and alcohol from liver disease nomenclature, although desirable, might be considered unlikely to happen, as aetiological and histopathological terms have a strong historical base within hepatology, including for non-stigmatised areas (eg, autoimmune hepatitis, viral hepatitis, DILI), but we need to strive towards their

appropriate implementation. Furthermore, although some names of liver diseases might not be inherently stigmatised, their transmission routes and the populations most at risk are—for example, injecting drug use and PWID with regards to chronic HCV infection. Although we do not wish to overstate its importance, we believe that the health of millions depends on urgently addressing how we converse about our patients and their diseases.

Helping European children navigate a rapidly developing marketing ecosystem

The strongest evidence for the impact of marketing comes from reviews of longitudinal and cohort studies of children, which consistently report that exposure to alcohol marketing increases the risk that young people will start to drink alcohol or, if they already drink, consume greater quantities.[355–358] In 2018, the EU Audiovisual Media Services Directive (AVMSD) implemented regulation on advertising for foods high in fat, salt, sodium, and sugars, and has strengthened the country-of-origin principle, rules for video-sharing platforms, protection of minors, and provisions to protect children from inappropriate audiovisual commercial communications.[359] Currently, however, the AVMSD does not account for alcohol advertising. There is strong evidence to support policies that reduce children's exposure to marketing, with those of complete and partial marketing bans being most effective.[26]

Children, young people, and vulnerable groups are the most susceptible to marketing messages and need to be protected from the marketing of both alcohol and ultra-processed foods, as well as high-fat, high-sugar, and high-salt foods (so-called HFSS foods). Current systems of self-regulation are ineffective, and transparent monitoring and reporting by public health agencies is required to ensure consistent enforcement and accountability.[360] Most European countries have marketing regulation policies to protect the youngest and most vulnerable segments of the population, ranging from complete bans to light-touch self-regulation—63% of European countries have statutory regulation, 34% have self-regulation, and 3% have coregulation.[361]

The 2011 Alcohol Act in Norway prohibits the marketing of alcohol almost entirely and has wide public and political support.[362] Lithuania implemented similar legislation in 2018, which includes a total ban on alcohol advertising with only minor exemptions, such as the logo of producers in sales areas.[363] In a compromise with industry, the Irish Public Health Bill from 2019 has key components for regulation to protect children, such as limits to the placement of adverts near schools or at public transport stops or stations, and alcohol adverts cannot be shown in cinemas showing films to those younger than 18 years. A similar compromise in France is the Loi Evin measure,[364] in which alcohol marketing requires action on both the advertising media used and the messages transmitted. The existence of these compromises shows that commercial forces remain strong.

The marketing landscape is rapidly evolving with the emergence of digital marketing. WHO reports that marketing on mobile phones increased from US$20 billion in 2013 to $200 billion in 2018.[365] Spending on digital marketing now exceeds that on television in many countries and is highly focused and largely immune from scrutiny. WHO has uncovered a rapidly evolving and complex digital marketing ecosystem, whereby individual so-called advertising impressions are traded within obscure interactions between networks of competing delivery agencies. The absence of reliable sources of age verification data means that the exposure of children to the marketing of unhealthy products is not prevented. WHO has proposed a range of technological solutions under the banner of CLICK, an acronym derived from: Comprehend the digital marketing environment, Landscape of campaigns, Investigate exposure, Capture on screen, and Knowledge sharing. The intention of these measures is for policy makers to start to understand and map the digital marketing environment, leading to transparency around the actual levels of exposure of children to individual brands and formal regulation of the digital ecosystem.

The principle that marketing bans work was first established for tobacco and framed into global law with the WHO Framework Convention on Tobacco Control.[366] Commercial operators are highly skilled at evading partial regulations; in an article subtitled *Marketing with the Lights Out*, the various evasion methods were revealed and include sponsorship, surrogate brand extensions, clothes branding, product placement, cross-border tourism, innovative packaging, and imaginative uses of direct digital communications.[367] This Commission strongly believes that the only effective solution will be a complete ban on all forms of alcohol marketing, including digital marketing, in keeping with SDG target 3.5 on addressing the prevention and treatment of harmful use of alcohol.

Labelling regulation is also relevant. A well known prototype example comes from Chile, where legal restrictions were imposed from 2016 providing firm restrictions to marketing and labelling.[368] The law constrains cartoon food packaging, prevents educational institutions from offering unhealthy products, restricts TV marketing, prohibits promotional toys, and forces producers to place black warning signs in their packaging in case they exceed the established limits of total sugar, saturated fats, or sodium. This approach has already resulted in a considerable reduction in the content of sugar, saturated fats, and salt.[369] The quest for Europe will not be as easy, as the most powerful lobbies have a deep reach and a long history of influencing policy making. Nonetheless, Europe needs the same type of leadership

in a much more politically complex setting, accounting for the fact that EU member states alone do not represent the whole of Europe.

The relationship between media use, family dynamics, and school environments on a child's likelihood to have overweight or obesity is an area of research with a paucity of empirical evidence but with an increasing appreciation of the genetic influence in how people respond to other obesogenic risk factors.[370] However, the scarce evidence for health literacy programmes, cognition, attitudes, and behaviours suggests a need for both better designed studies and more effective interventions.[371] Once obesity occurs, it is very difficult to reverse it; in long-term, randomised, controlled trials, the greatest weight reduction occurs within the first 6 months of diets followed by weight regain in most people.[372,373] Hence a focus on prevention at the earlier stages of life, such as childhood, has a greater potential impact.

This is not the sole reason for targeting school children. In a given environment, food, transport, land use, and urban environments are macrosystems that, in turn, influence the intermediate systems in which people interact, which are mainly schools, workplaces, and community spaces. These intermediate systems, in turn, influence microsystems such as families and social groups, changing their behavioural patterns. A change in microsystems or intermediate systems is easier to achieve and can have sustainable and measurable targets, while providing a starting point for a change in macrosystems from the inside (ie, think globally, act locally). At the time of writing, more than 50% of the global population lives in cities with more than 500 000 inhabitants, and two-thirds of people with type 2 diabetes live in urban areas, with an increased risk of NCDs (termed urban diabetes). Making cities and human settlements inclusive, safe, resilient, and sustainable (SDG 11) has the potential to reduce inequalities (SDG 10.2) and the prevalence of NCDs, including NAFLD.

Children represent the crossroads between families and schools (microsystems and intermediate systems) and community policies, and actions to improve children's health are generally well supported by public opinion. In addition to their role as pupils receiving education in schools, children might also have a role in promoting sustainable changes within local communities. For example, fostering specific educational programmes involving academia, local governments, schools, children, and their families might help to translate knowledge into action by children themselves, who are encouraged to be teachers to other children and their families. These programmes should be age-specific, with a special focus on adolescence as a period of flux in relation to health-related behaviour, and should engage all people across the socioeconomic spectrum.

Although educational programmes in overcoming obesity are unlikely to be effective as interventions on their own,[170,371] there are studies reporting the effectiveness of parent-based interventions on healthy eating and active behaviours in preschool children.[374] A systematic review that included 19 studies found that school-based interventions for obesity prevention and promotion of physical activity and fitness have the potential to be more effective if they prioritise physical activity than if they do not.[375] A Cochrane review showed that physical activity interventions designed for childhood weight management exhibited benefits on mathematics achievement,[376] executive function, and working memory, whereas only multicomponent interventions focusing on both physical activity and healthy diet in children with obesity could deliver benefits in general school achievement.[376]

Similar to the treatment approach in other chronic diseases, health-care providers should discuss the broader picture of complications with their patients with liver disease; the message should be that risk reduction of end-stage liver disease, liver cancer, diabetes, and cardiovascular disease is possible. These messages and supportive information and education can also be delivered through patient groups and associations. In a cross-sectional study among 146 patients with NAFLD, healthier nutritional behaviour was associated with higher patient understanding of NAFLD.[377] A qualitative study[378] highlights the important role of health-care providers as educators on the significance of NAFLD (in itself and in the broader context of the metabolic syndrome) and its potential to regress, teaching healthy eating skills and enhancing confidence in the benefits of diet.[379] Among 3822 people with NAFLD (fatty liver index of at least 30) from the US National Health and Nutrition Examination Survey (2001–14), only 54% intended to lose weight, even though more than 95% had overweight or obesity. Notably, among those who tried to lose weight, only up to 10% (with lower rates among men than among women) attended weight loss programmes.[380] Education makes an important contribution but is insufficient on its own; it should be one aspect of a broad package of measures that include comprehensive, accessible, and affordable care and the creation of healthy environments.

Viral hepatitis elimination in Europe

The World Health Assembly has promulgated a strategy for the elimination of viral hepatitis as a component of the 2030 Agenda for Sustainable Development. The aim is to reduce annual deaths from viral hepatitis by 65% and new infections by 90%, thus saving 7·1 million lives globally by 2030. To achieve these goals, two age-dependent interventions are key: prevention of neonatal and childhood infection by HBV vaccination and, secondly, prevention of cirrhosis and hepatocellular carcinoma in adults by appropriate

	Publicly funded screening programmes		Coverage of harm-reduction programmes*		Viral hepatitis treatment		Non-prescriber type restrictions†	
	Hepatitis C	Hepatitis B	Needle and syringe programmes	Opioid agonist therapy	Direct-acting antivirals reimbursed	Entecavir and tenofovir disoproxil fumarate reimbursed	Hepatitis C	Hepatitis B
France	🟢	🟢	🟡	🟢	🟢	🟢	🟢	🟢
Germany	🟡	🔴	ND	🟢	🟢	🟢	🟢	🟢
Greece	🟢	🔴	🟡	🟢	🟢	🟢	🔴	🟢
Hungary	🟢	🟢	🟡	🟡	🟢	🟢	🔴	🔴
Italy	🟢	🔴	ND	🟡	🟢	🟢	🔴	🔴
Poland	🟡	🟡	ND	ND	🟢	🟢	🔴	🔴
Romania	🟢	🟢	🟡	🟡	🟢	🟢	🔴	🔴
Spain	🟢	🟢	🟡	🟢	🟢	🟢	🔴	🔴
UK	🟢	🟢	ND	🟢	🟢	🟢	🟢	🔴
Armenia	🟢	🟢	🟡	🟡	🟢	🟡	🔴	🔴
Azerbaijan	🟡	🟡	🟡	🟡	🟡	🟡	🟢	🟢
Belarus	🟢	🟢	🟡	🟡	🟢	🟡	🔴	🔴
Georgia	🟢	🟢	🟡	🟡	🟢	🔴	🔴	🔴
Kazakhstan	🟢	🟢	🟡	🟡	🟢	🟢	🔴	🔴
Kyrgyzstan	🔴	🟡	🟢	🟡	🟢	🟡	ND	🟢
Moldova	🟡	🟡	🟡	🟡	🟢	ND	🟢	ND
Russia	🟡	🟡	🟡	🔴	🟡	🟡	🔴	🔴
Tajikistan	🔴	🔴	🟢	🟡	🟢	🟢	ND	ND
Ukraine	🟡	🟡	🟡	🟡	🟢	🟡	🔴	🔴
Uzbekistan	🟡	🟡	🟡	🔴	🟡	🔴	🟢	🟢

Figure 21: **Progress towards key viral hepatitis elimination targets in the most heavily burdened countries in Europe**
Green circles: yes; yellow circles: partial; red circles: no; unless otherwise stated. *Harm-reduction coverage estimates obtained from Larney et al;[381] green: adequate coverage (based on WHO recommended levels: >200 needles and syringes distributed per PWID per year and >40 recipients of opioid agonist therapy per 100 PWID); yellow: available but inadequate (below WHO recommended levels); red: not available; ND: available but no data on coverage. †Refers to prescriber-type restrictions for reimbursment of viral hepatitis treatment; green: no restrictions; red: specialist only; ND: no data. PWID=people who inject drugs.

diagnosis and treatment. Only a few high-income countries in Europe are projected to meet the WHO HCV mortality targets by 2030 (France, Germany, Iceland, Italy, Spain, Sweden, Switzerland, and the UK);[185] others are not expected to meet these targets with 9 years remaining. The current status for key indicators of progress in different countries is each listed in figure 21.

The WHO viral hepatitis elimination aims are, however, achievable. Prevention of incident chronic HBV infection is being attained by universal birth dose HBV immunisation and appropriate treatment of HBsAg-positive mothers in the third trimester of pregnancy to prevent mother-to-child transmission; substantial progress has been made.[382] Almost all countries in the WHO European Region (92%) have successfully implemented universal childhood HBV immunisation programmes with excellent coverage of three doses of the HBV vaccine (at least 90%). However, some low-endemic countries (eg, Denmark, Finland, Iceland, and Sweden) have not implemented a universal vaccination programme and rely on selective immunisation of people at high risk of HBV infection. This Commission recommends that all European countries implement universal childhood HBV vaccination and monitor its compliance, particularly in neonates of marginalised populations, or migrants, refugees, and asylum seekers. The revised WHO recommendations to prevent mother-to-child transmission mandate testing for HBsAg and HBV DNA to identify mothers with viraemia requiring care, and can be linked to clustered family screening.[383] Screening of pregnant women for HCV, in addition to HIV and HBV, offers a unique means to identify young women with chronic hepatitis and provide timely treatment.[384] Universal birth dose vaccination is an imperative (a first dose of HBV vaccine preferably within 24 h of birth to all infants, followed by two or three doses to complete immunisation), and HBV vaccination coverage among high-risk populations, such as people who are incarcerated, PWID, men who have sex with men, and sex workers, require amplification.

Highly effective antiviral agents against HBV and HCV have the potential to drastically reduce morbidity and mortality.[52] In western Europe, where surveillance data have documented a decline in prevalence of HCV and a reduction in admission for the consequences of chronic viral hepatitis, substantial progress has been made towards the WHO elimination targets. However,

***Panel 2*: Actions to address the pricing barrier for viral hepatitis drugs**

- Actual negotiated prices should be publicly available; allowing countries to know and harmonise prices in the 44 countries in Europe can help to drive down prices
- All countries in Europe should have access to source data that provides an up-to-date range of prices in different European countries for sofosbuvir and ledipasvir (Harvoni), sofosbuvir and velpatasvir (Epclusa), glecaprevir and pibrentasvir (Maviret), grazoprevir and elbasvir (Zepatier), and sofosbuvir, velpatasvir, and voxilaprevir (Vosevi); keeping real prices confidential reduces incentives and possibilities
- Shared procurement should be a priority in Europe; procurement mechanisms could be put in place to deliver direct-acting antivirals at an affordable price, as recommended in the Global Fund guidelines for grant budgeting for health products[397]
- By the end of 2018, global sales of hepatitis C virus (HCV) direct-acting antivirals reached US$87 billion, such that companies have more than recouped their research and development costs; pharmaceutical companies play a pivotal part in providing medicines but need to balance shareholder needs with responsibility to patients
- There is a need to strengthen governments' hands and provide a sense of purpose and collective organisational strategy for governments and the pharmaceutical industry to fully utilise the benefits of breakthrough HCV therapies

surveillance data to track progress are poorly collected in much of Europe, which presents an obstacle to establishing gains. To realise the promise of antiviral therapy to further reduce incidence, collaborative and innovative stakeholder partnerships are needed to devise new strategies to raise awareness, scale up test-and-treat strategies in community-based settings, and increase access to harm-reduction services (eg, oral substitution therapy and needle and syringe exchange programmes).

As expected, a higher prevalence of chronic HBV infection has been observed in migrant populations from endemic regions, including sub-Saharan Africa and the Middle East. Most migrants with HBV or HCV are not aware of their status. The continued influx of migrants, refugees, and asylum seekers to Europe poses health challenges but also provides an opportunity for health gain. The majority of them are younger than 35 years. Proactive testing and treatment for chronic viral hepatitis provides an important opportunity to ensure entry to health-care systems in their country of adoption[385] and might contribute to an increase of their health awareness, work productivity, and social assimilation.[386] In the pursuit of universal access to health care for all immigrants, European nations need to adopt unified policies to testing and treatment for viral hepatitis of newly arrived immigrants, including those who are undocumented.[387]

European countries with universal health coverage, such as Spain, France, and the UK, have made progress by developing national plans outlining agreed elimination goals, strategies to achieve those goals, and indicators to track progress. Similarly, Georgia has an ambitious national HCV elimination plan, with surveillance and modelling undertaken to assess interim progress.[388] These existing national plans can be adapted to assist the modelling and development of surveillance strategies and well funded action plans in several eastern European countries, Russia, and some former Soviet republics, which have still not prioritised viral hepatitis as a public health threat. Numerous cost-effective and economic analyses have underpinned viral hepatitis policies, including screening in pregnancy,[389,390] technology assessments for direct-acting antiviral therapy,[391] investment frameworks for finding and treating viral hepatitis,[392] vaccination,[148,393] pricing,[394] and scaling up prevention test-and-treat efforts.[395,396]

Treatment as prevention is pivotal but can only be achieved by proactive outreach and widespread test-and-treat approaches. We propose reducing costs and improving access to treatment by enhancing transparency and universal disclosure of antiviral pricing within Europe. This disclosure would highlight discrepancies, in contrast to the current concealment of national prices behind national protective procurement dealings that cite commercial sensitivities. Lower pricing would incentivise the evaluation of greater treatment access, resulting in net benefit to originators and to public health elimination strategies (panel 2).

Injection drug use is the main driver of HCV transmission in Europe,[37] highlighting the importance of PWID-targeted interventions. Substantial investment in harm-reduction services is needed, and all restrictions to harm-reduction programmes should be lifted. New initiatives are required to assist the surveillance of viral hepatitis in PWID[398] and reduce the punitive stigmatisation of this group. Improving the currently suboptimal coverage and inadequate provision of needle exchange and opioid agonist therapy programmes is crucial to reducing the incidence of HCV infection and improving HCV treatment uptake.[381,399–401] Peer workers' programmes to navigate vulnerable individuals toward test-and-treat programmes are invaluable adjuncts.

Micro-elimination is a strategic approach to eliminating HCV in particular groups, which can be expanded to reduce national incidence and even global prevalence.[402,403] The approach targets specific subpopulations with an elevated HCV prevalence or geographical settings for HCV elimination. Subpopulations of interest might include those most marginalised, such as PWID or people who are incarcerated, or those co-infected with HIV, people with haemophilia, and patients on chronic dialysis. The four key components defining micro-elimination are having a plan, achievable time-bound targets, a multistakeholder process, and ongoing

monitoring; all in line with the WHO Global Health Sector Strategy. Examples of micro-elimination programmes in progress include testing and treatment for HCV in HIV-infected men who have sex with men[404] and testing in prisons.[405,406] However, micro-elimination of HCV has had limited success in many countries, and national data reporting the effect of micro-elimination in Europe are sparse. Micro-elimination is more difficult to apply in HBV infection, but universal vaccination, testing, and treatment have reduced the expected mortality from HBV in regional initiatives in large target populations.[407]

Thus, current levels of diagnosis and treatment demand a challenging expansion to meet WHO HCV elimination targets.[408] All archaic treatment restrictions should be lifted. Many patients require diagnosis and assessment, which have become more challenging as historical treatment groups have shrunk in high-income countries. Quality linkage programmes should be put in place to ensure reflex testing for HCV RNA and appropriate linkage to care. Prison testing should provide an opportunity for opt-out testing. Widespread regular testing of HIV-positive and HIV-negative men who have sex with men for HCV in conjunction with HIV pre-exposure prophylaxis programmes is required to ensure early detection of de novo and recurrent infection in those engaging in high-risk activities. Testing high-risk groups alone, however, will not satisfactorily diagnose 90% of all viral infections, and initiatives to find all adults are required—hence our proposal to link viral hepatitis testing to current COVID-19 surveillance programmes (table 3).

One Europe: defragmentation of the European policy landscape

The changes to health systems, testing and treatment, research priorities, and health policy suggested throughout this Commission report should be implemented without fragmentation at a pan-European level.[409,410] The idea of a Biomedical Advanced Research and Development Agency or a European Health Emergency preparedness and Response Authority (HERA) has been debated in the European Commission since early autumn, 2020; HERA was launched on Sept 16, 2021, and is envisaged to be fully operational by 2022.[411,412] While focusing on responses to cross-border infectious threats and emergencies, inspired by the COVID-19 pandemic, the concept of unified and coordinated approaches "across the whole value chain" and the development of "strategic investments for research, development, manufacturing, deployment, distribution and use of medical countermeasures"[411] hold considerable relevance also for non-infectious risks, NCDs and the liver disease syndemic. Although the *Lancet* Commission on liver disease in the UK has provided important model examples on policy interventions at a single country level,[12] we have, throughout this report, shown the benefits that would result from taking a pan-European perspective to similar interventions.[409,410,413] The policies that regulate consumption patterns of products involved in liver disease development, including ultra-processed foods, alcohol, and added sugar, are crucial prototypes for this principle point[13] and in urgent need of anchoring at a broader European level, similar to that of policies to control tobacco use.

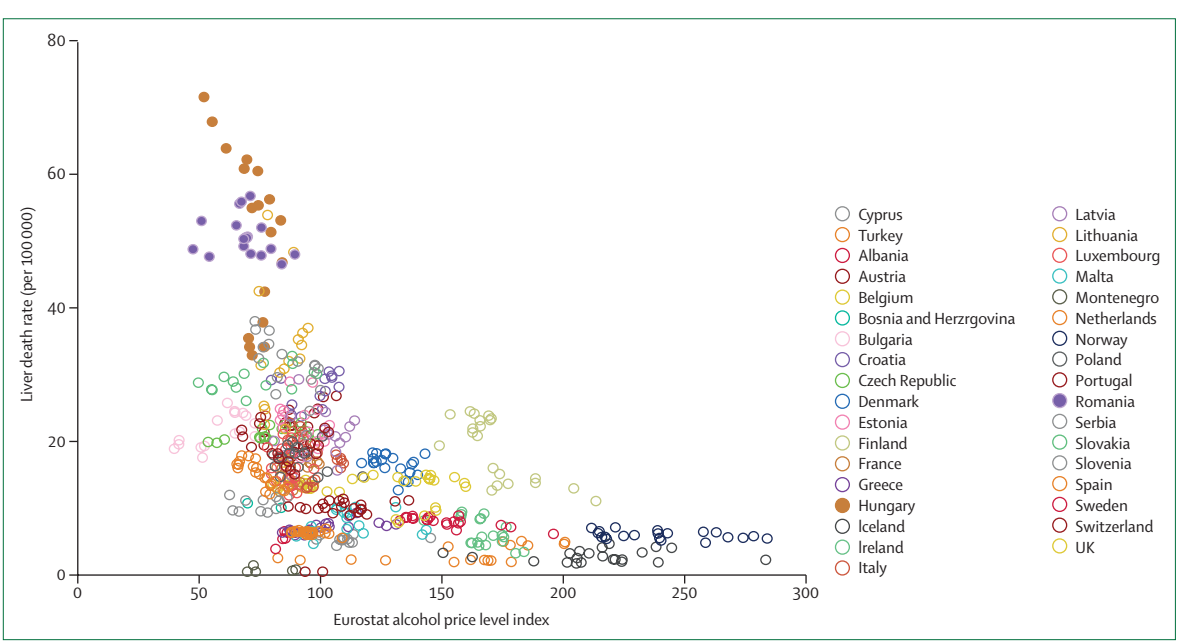

Figure 22: **Association between the price of alcohol and liver death rates across selected European countries in 2010**
Data taken from a range of European countries show an inverse exponential association between the price of alcohol and liver death rates across countries, suggesting that raising the price of alcohol can be one of the most effective policies to combat alcohol-related liver disease (appendix p 19). Analysis by Nick Sheron.

Within the WHO European region, there is an inverse relation between the price of alcohol and liver-related mortality rates (figure 22), supporting the health benefits of harmonising alcohol taxes at a higher level.[14] For instance, in Finland, rapid increases in liver-related mortality occurred when Estonia joined the EU and import controls were relaxed, leading to an influx of cheap alcohol, but a subsequent increase in alcohol tax and changes in alcohol availability reduced consumption and consequently liver-related mortality.[21] Since 1980, UK liver death rates have increased by a factor of four, closely tracking changes in the affordability of alcohol (appendix p 37) and showing the responsiveness of liver-related mortality to relatively small changes in alcohol taxation.[414] These country-level experiences should inspire the establishing of European standards for policy measures to control associated health threats.

Various types of price regulation and taxation strategies have been shown to be effective and cost-effective,[415,416] and the social policy experiment of minimum unit pricing in Scotland reinforces its effectiveness, especially in terms of reducing health inequalities.[15] The evidence for minimum unit pricing is robust and comes from several sources;[26,417] for example, from a series of natural experiments and modelling studies across the UK, Ireland, the Czech Republic, and Germany, which were able to estimate the longer-term effects of a minimum unit pricing policy.[28,418–420] Taken together, these studies consistently show that minimum unit pricing is effective at reducing alcohol consumption, hospital admissions, deaths, criminal offences, and workplace absence. By effectively targeting the cheap alcohol that is purchased by those with the highest alcohol intake, minimum unit pricing results in the greatest health and social gains for the least affluent groups.

Legal challenges led by the alcohol industry have been turned down by unanimous verdicts from the European Court of Justice and the UK Supreme Court, which both judged minimum unit pricing to be more effective than comparable measures because it is targeted at those with the highest alcohol intake, and geared towards reducing health inequalities.[421] Natural experiments in minimum unit pricing underway in Scotland, Ireland, and Russia will provide more data on the impact of such measures and influence policy in Europe.

Other effective policies to reduce alcohol consumption and alcohol-related harm include marketing regulations and ideally a complete marketing ban, such as those seen in Norway and Lithuania, with the effectiveness of marketing regulation reducing as any advertising ban moves from a complete ban (covering print and non-print media and online media) to a partial ban (including only one media type for example). Our Commission believes that the EU should step up to this challenge and impose pan-European regulations to all forms of alcohol marketing, expanding on the AVMSD and building on the experiences from other areas of pan-European legislation, such as the General Data Protection Regulation.

Taxation for added sugar and ultra-processed foods is currently being implemented in some European countries,[422] and this Commission strongly recommends that these efforts are harmonised across Europe. Sugar-sweetened beverage levies are the most prominent and there is consistent evidence regarding the beneficial impact on reducing consumption in several policy evaluations.[16] Multinational corporations put up considerable resistance to efforts to adapt to national, social, and political requirements. This resistance can only be overcome by coordinated actions across countries. Proposed policies certainly do not only impact liver health, hence their widespread adoption should be a priority in new EU legislation over the next decade. Tobacco regulations exemplify how the combination of strict taxations, and packaging and advertisement control lead to reductions in disease-specific incidence and premature mortality. In plain words, European countries should address unhealthy foods and drinks with the same uniform approach.

The WHO has recommended so-called best buys—evidence-based policies for tackling the drivers of NCDs—and one of the most recommended measures is mandatory front-of-pack labelling. This measure is an important policy tool for countries to help consumers make healthier food choices and to reduce total intake of energy, sugar, sodium, and saturated fat.[423–425] Voluntary food labelling schemes, currently present in many European countries, are insufficient, resulting in poor adherence from food manufacturers. Countries that do have food labelling policies use different schemes and regulations, resulting in confusion and inconsistency across the continent. The implementation of a European-wide, mandatory, government-led, simple, informative, and uniform front-of-pack labelling approach based on the latest scientific research and guidelines would help encourage consumers to reduce their intake of ultra-processed foods (and, in turn, saturated fat, sugar, and salt). WHO guidelines and recommendations also state that labelling should be accompanied by supporting initiatives to aid implementation by the industry and public.[423] In addition, formal and comprehensive policy monitoring and evaluation programmes are needed across Europe to assess impact, such as purchasing and consumption changes, nutritional knowledge in consumers, and potential health benefits, as well as the extent to which food manufacturers reformulate their products to become healthier to avoid unfavourable nutritional labelling.

Reformulation to reduce sugar content in food or labelling to reduce purchase of high-sugar foods can have a great impact on NAFLD prevention, as suggested

from clinical studies and also as strongly supported by our analysis of the OECD data. Food labelling alone is unlikely to be sufficiently effective without an accompanying impact on food reformulation, making collaboration with the food industry imperative. In controlled trials, reduced sugar consumption among children led to a regression of NAFLD within a short time (weeks),[426,427] whereas inaction was shown to lead to situations in infants for which, at the age of 1 year, those consuming more than two sugar-containing beverage servings per day were 3 times more likely to develop NAFLD at the age of 10 years than those consuming less than one serving per day. The association was independent of BMI and was strongest among children from mothers with a lower level of educational attainment.[169]

All measures to target obesity will have a major beneficial effect in preventing NAFLD development and related complications, but will require concerted efforts if they are to be successful. A WHO meta-analysis of 11 systematic reviews on the effectiveness of fiscal policies to reduce bodyweight, improve diet, and prevent chronic diseases (including NCDs) concluded that the strongest evidence to date was for sugar-sweetened beverage levies, reducing consumption by 20–50%.[428] A national study,[429] modelled on a 20% levy on sugar-sweetened beverages in the UK, estimated that it would prevent 3·7 million cases of obesity and 25 498 cases of BMI-related disease over the next 10 years (2015–25). These examples should set important directions for European health policy going forward, supporting, at a European level, the work of previous *Lancet* Commissions.[12,13,15,430]

Future perspectives

During the past decades, hepatology has been transformed from a field of therapeutic nihilism to one with some of the greatest successes in modern medicine, including a vaccine against cancer (in the form of hepatocellular carcinoma as a complication to HBV) and the first chronic viral infection to be cured by medical therapy with oral drugs (HCV). Although such developments will certainly help address part of the burden of liver diseases in Europe, there are problems still to be resolved. A major emerging challenge is that any improvement in diagnosis and care of liver disease and associated comorbidities will not be successful in reducing the burden of liver disease mortality if it is not accompanied by an effort to target the most disadvantaged communities.

We will have to keep moving the focus towards health promotion and the prevention of liver diseases and also diagnose these conditions at much earlier stages, so as to prevent the development of end-stage liver disease with its costly and life-threatening complications (figure 4). Here, primary care and community health-care settings have a crucial part to play in outreach, referring and filtering patients with benign or irrelevant abnormalities in liver blood tests from patients at risk of progressive fibrosis, aided by technology in promoting streamlined care, automated investigation in response to mild abnormalities, and increased access to second line—and second generation—fibrosis testing.

There will continue to be a huge unmet need for health-care professionals looking after people with liver disease, and only a minority of these will be hepatologists. The health burden caused by liver diseases will only be ameliorated if this challenge is taken as a multidisciplinary task and with the involvement of communities that are the most concerned with liver disease. Enabling primary care to identify patients at risk of and with liver disease and to implement proposed algorithms for fibrosis screening will be crucial. The gastroenterologist, when taking care of patients with inflammatory bowel disease, must keep an eye on the bile ducts and should not miss primary sclerosing cholangitis. The endocrinologist should not miss NAFLD and should be aware that people with type 2 diabetes have a significantly increased risk of advancing liver fibrosis and hepatocellular carcinoma. The oncologist should be aware of metastatic liver disease and be knowledgeable of DILI caused by the anti-cancer drugs, in particular when using checkpoint inhibitors. The haematologist should not miss haemochromatosis and should think of cirrhosis when patients present with thrombocytopenia. The neurologist should refer any patient with Wilson's disease to the hepatologist and should not miss hepatic encephalopathy. And, importantly, the close relationship between liver disease and mental health warrant attention, as psychiatric disorders such as depression are highly prevalent in people with liver disease and strongly affect engagement in care.[431] If all disciplines work together and proactively seek to intervene at early disease stages, the burden of liver disease complications will decline. Specialty protectionism should be challenged; it should be considered as appropriate that the diabetologist manages people with NAFLD and an oncologist manages patients with liver cancer. Our priority should be to ensure that people with liver disease access the best care, not the terms of our profession. This approach will require the development of interdisciplinary and multiprofessional teams focusing on patient-centred training and care, and which should be supported by electronic systems and the developing telemedicine tools. However, it also requires a change in the way health care is funded and reimbursed, which is principally a political problem and without which health inequalities will remain a major challenge.

The multidisciplinary composition of this Commission, with nurses and patients included, reflects the orientation that is needed to overcome many of the barriers highlighted for our recommendations (table 2). Responsibilities reside at multiple levels, and messages provided

throughout this document have a diverse target audience. More than anything, we wish for the document to serve as a resource base for all those wishing to improve the conditions for patients with liver disease, including politicians, physicians, nurses, and the patients themselves, and to prevent the many premature deaths occurring throughout Europe every year. Due to restrictions of space and time, many topics warrant in-depth work and further investigation in the future, those related to health inequalities and multidisciplinary care most of all. Some of this work might reside with the team responsible for this report, while some of the ensuing work warrants considerations for separate Commissions and academic research projects. The work should explicitly account for sex-related differences in risk factors, protective or aggravating effects of sexual hormones, and variances linked to genetics and physiological differences between men and women to achieve truly individualised management for patients at risk of liver disease.[432]

There are many stakeholders within the health-care system to involve in the follow-up of this report, including both primary and secondary care, and their involvement requires coordination and integration. We believe EASL needs to step up to this responsibility and continue its outreach to other learned societies (eg, the European Association for the Study of Diabetes and the European Association for the Study of Obesity[433]) in forming the necessary partnerships, with primary care and nurses in particular, and promote interdisciplinary and team-based work. Disease competition and the positioning of roles and responsibilities throughout the care cascade for people with liver disease belongs in the past, and patient needs and the patient voice should be the nucleus around which health systems and health-care amendments should be built. Patient organisations, such as those participating in this Commission, can help in bridging some of the gaps. Monitoring of impact remains an integral part to these future steps, and the major gaps in data surrounding liver diseases must be overcome as a centrally important part of this monitoring.

With the ageing European population, the incidence of hepatocellular carcinoma will continue to grow, and early diagnosis is critical to enable curative treatment. The promising developments of new medical therapies for hepatocellular carcinoma will improve survival even for people at advanced stages of disease. A particular future challenge is cholangiocarcinoma, which is on the rise in Europe and in many parts of the world. Gene sequencing of tumour tissue leading to targeted molecular and personalised therapies has provided some hope for patients with cholangiocarcinoma, and general improvements in medical oncology, immunotherapy included, are slowly being applied also to liver cancer. Liver surgery will continue to evolve, with minimal invasive procedures being widely used to treat curable liver cancers. Although regenerative medicine is likely to provide opportunities in people with end-stage and acute liver failure, only the future will tell whether the dream of artificial liver systems for long-term organ replacement will finally become reality. In the future, we will see cellular and stem-cell therapies in a variety of forms representing this shift.

The emphasis of this Commission report has been on the working age population and young Europeans. We nevertheless face an era in which European populations are ageing more than any other region in the world.[434] Due to changing demographics, a decreasing working age population has to support health care for an increasing population of retired people suffering from costly chronic diseases, including chronic liver diseases and their complications. This shift will increasingly challenge health-care systems throughout Europe and might also contribute to stigmatisation of older people.

The field of liver transplantation will drastically change, as organ shortages will probably become more of an issue. More than 150 000 liver transplantations have been done in Europe since the start of the programmes in the early 1980s, and more than 100 000 of these patients are still alive. The age of donors and recipients will continuously increase, leading to an acceleration of fibrosis progression in the transplanted livers. The technique of orthotopic liver transplantation has not changed over the past decades, nor has immunosuppression with all its current side-effects. Donations after cardiac arrest is a topic predominantly driven by hepatology, and developments in live donor transplants, auxiliary transplants, machine perfusion, and liver support devices are likely to expand opportunities in end-stage liver disease management. Finally, in orthotopic liver transplantation, long-term tolerance must be sought by the weaning of toxic immunosuppressive drugs and the development of strategies for personalisation of immunosuppression.

We are likely to see an increased attention to the role of toxic exposures in the development of liver diseases, including drugs and occupational hazards.[435] DILI as a medical example will further increase in prevalence as the number of drugs developed will continuously grow. Every 7 years, the number of compounds produced by the chemical industry doubles, and most of them are metabolised by the liver, creating the potential for acute, subacute, or chronic DILI. We will certainly see new entities of DILI in the future as we have recently seen by the advent of immune-mediated DILI caused by modern biologicals used in many disciplines, including oncology, rheumatology, gastroenterology, neurology, and dermatology.

Most of all, this Commission aims to show how liver health is a window to the general health challenges of Europe in the 21st century. The risk factors for liver disease—alcohol, obesity, and intravenous drug use—reflect behaviours and conditions that are the

consequence of both unhealthy environments and social inequities. Addressing these problems requires bold and extensive public health responses, but these measures are often opposed by commercial interests that prioritise the financial health of their shareholders and employees over the health of the European population.

The COVID-19 pandemic has exposed the weaknesses of European health systems, which are ill equipped to fight such public health challenges. Europe's public health response to COVID-19, as for other threats, has been dominated by wide variations and poor coordination. This Commission calls for a different kind of European response: integrated, coordinated, and effective. As we recover from the COVID-19 pandemic, we must seize the opportunity to improve the health of our populations. Changing the ways we address the risk factors for liver disease could function as a sentinel for the health of the European population, increasing solidarity and unity across all EU member states and the entire European region.

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THK, NSh, SZ-S, GD, EB, RP, SJH, BSa, NKM, MS-B, HY-J, MN, TRe, RF, MYS, VM, HC-P, DK, JVL, PG, MB, PNN, PB, and MPM were involved in conceptualisation and participated in formal meetings of the EASL-*Lancet* Commission on liver disease in Europe. THK, NSh, SZ-S, PC, GD, EB, RP, SJH, BSa, NKM, AB, MS-B, CYP, NSc, MH, HJV, ES, GM, HY-J, DB, MN, TRe, AT, TRh, CT, CP, CS, RF, MYS, AP, PJ, AC, IG, CL, EP, NF, JMM, VM, HR, HC-P, DK, RB, JVL, PG, MB, PNN, PB, and MPM participated in the working groups. NSh, SZ-S, GD, EB, RP, SJH, BSa, NKM, MC, MAD, AB, MS-B, CYP, BSh, AL, MD, NSc, MH, AT-S, AT, PJ, AC, VM, DK, RB, MB, and PNN were involved in accessing and curating the data. NSh, SZ-S, GD, EB, RP, SJH, BSa, NKM, MC, MAD, BSh, AL, MD, NSc, MH, AT-S, DK, RB, MB, and PNN were involved in the statistical analysis, and interpretation and visualisation of the data. THK, NSh, SZ-S, PC, GD, EB, RP, SJH, BSa, NKM, MC, AB, MS-B, CYP, NSc, MH, HJV, ES, AT-S, DB, TRh, CT, CP, CS, AP, IG, EP, NF, ATM, DK, RB, JVL, PG, MB, PNN, PB, and MPM provided original draft contributions to the writing of the report. NSh, JVL, RP, EB, PNN, MB, DK, BSa, and PG were working group leaders. THK, PNN, PB, and MPM were involved for the overall supervision and project administration. All authors reviewed and edited the report, and approved the final version of the manuscript for publication.

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References

1 Karlsen TH, Tacke F. "The times they are a'changin'"—positioning the European Association for the Study of the Liver in the changing landscape of hepatology. *J Hepatol* 2018; **68:** 873–75.

2 Manns MP, Burra P, Sargent J, Horton R, Karlsen TH. The *Lancet*–EASL Commission on liver diseases in Europe: overcoming unmet needs, stigma, and inequities. *Lancet* 2018; **392:** 621–22.

3 Manns MP, Buti M, Gane E, et al. Hepatitis C virus infection. *Nat Rev Dis Primers* 2017; **3:** 17006.

4 Baumert TF. The Nobel Prize in medicine 2020 for the discovery of hepatitis C virus: transforming hepatology. *J Hepatol* 2020; **73:** 1303–05.

5 Kleinert S, Horton R. Obesity needs to be put into a much wider context. *Lancet* 2019; **393:** 724–26.

6 Horton R. Offline: COVID-19 is not a pandemic. *Lancet* 2020; **396:** 874.

7 Cooke GS, Andrieux-Meyer I, Applegate TL, et al. Accelerating the elimination of viral hepatitis: a *Lancet Gastroenterology & Hepatology* Commission. *Lancet Gastroenterol Hepatol* 2019; **4:** 135–84.

8 Wagner EH. Chronic disease management: what will it take to improve care for chronic illness? *Eff Clin Pract* 1998; **1:** 2–4.

9 Tsochatzis EA, Newsome PN. Non-alcoholic fatty liver disease and the interface between primary and secondary care. *Lancet Gastroenterol Hepatol* 2018; **3:** 509–17.

10 Townsend SA, Newsome PN. The role of a dedicated non-alcoholic fatty liver disease clinic in 2016. *Dig Dis* 2017; **35:** 371–76.

11 Moodie R, Stuckler D, Monteiro C, et al. Profits and pandemics: prevention of harmful effects of tobacco, alcohol, and ultra-processed food and drink industries. *Lancet* 2013; **381:** 670–79.

12 Williams R, Aspinall R, Bellis M, et al. Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. *Lancet* 2014; **384:** 1953–97.

13 Williams R, Aithal G, Alexander GJ, et al. Unacceptable failures: the final report of the *Lancet* Commission into liver disease in the UK. *Lancet* 2020; **395:** 226–39.

14 Pimpin L, Cortez-Pinto H, Negro F, et al. Burden of liver disease in Europe: epidemiology and analysis of risk factors to identify prevention policies. *J Hepatol* 2018; **69:** 718–35.

15 Swinburn BA, Kraak VI, Allender S, et al. The global syndemic of obesity, undernutrition, and climate change: *The Lancet* Commission report. *Lancet* 2019; **393:** 791–846.

16 Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; **396:** 1204–22.

17 Mokdad AA, Lopez AD, Shahraz S, et al. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. *BMC Med* 2014; **12:** 145.

18 Maucort-Boulch D, de Martel C, Franceschi S, Plummer M. Fraction and incidence of liver cancer attributable to hepatitis B and C viruses worldwide. *Int J Cancer* 2018; **142:** 2471–77.

19 Hagström H, Adams LA, Allen AM, et al. Administrative coding in electronic health care record-based research of NAFLD: an expert panel consensus statement. *Hepatology* 2021; **74:** 474–82.

20 WHO. Global status report on alcohol and health 2018. Sept 27, 2018. https://www.who.int/publications/i/item/9789241565639 (accessed Nov 4, 2021).

21 Sheron N. Alcohol and liver disease in Europe—simple measures have the potential to prevent tens of thousands of premature deaths. *J Hepatol* 2016; **64:** 957–67.

22 Haldar D, Kern B, Hodson J, et al. Outcomes of liver transplantation for non-alcoholic steatohepatitis: a European Liver Transplant Registry study. *J Hepatol* 2019; **71:** 313–22.

23 Jochmans I, van Rosmalen M, Pirenne J, Samuel U. Adult liver allocation in Eurotransplant. *Transplantation* 2017; **101:** 1542–50.

24 Ndugga N, Lightbourne TG, Javaherian K, et al. Disparities between research attention and burden in liver diseases: implications on uneven advances in pharmacological therapies in Europe and the USA. *BMJ Open* 2017; **7:** e013620.

25 Rehm J, Taylor B, Mohapatra S, et al. Alcohol as a risk factor for liver cirrhosis: a systematic review and meta-analysis. *Drug Alcohol Rev* 2010; **29:** 437–45.

26 Burton R, Henn C, Lavoie D, et al. A rapid evidence review of the effectiveness and cost-effectiveness of alcohol control policies: an English perspective. *Lancet* 2017; **389:** 1558–80.

27 WHO. European action plan to reduce the harmful use of alcohol 2012–2020. 2012. https://www.euro.who.int/__data/assets/pdf_file/0008/178163/E96726.pdf (accessed Nov 4, 2021).

28 Organisation for Economic Co-operation and Development. Preventing harmful alcohol use. May 19, 2021. https://doi.org/10.1787/6e4b4ffb-en (accessed Nov 4, 2021).

29 Pitcher AB, Borquez A, Skaathun B, Martin NK. Mathematical modeling of hepatitis C virus (HCV) prevention among people who inject drugs: a review of the literature and insights for elimination strategies. *J Theor Biol* 2019; **481:** 194–201.

30 Duffell E, Cortez-Pinto H, Simonova M, et al. Estimating the attributable fraction of cirrhosis and hepatocellular carcinoma due to hepatitis B and C. *J Viral Hepat* 2021; **28:** 1177–89.

31 Hope VD, Eramova I, Capurro D, Donoghoe MC. Prevalence and estimation of hepatitis B and C infections in the WHO European Region: a review of data focusing on the countries outside the European Union and the European Free Trade Association. *Epidemiol Infect* 2014; **142:** 270–86.

32 WHO. Web Annex 1. Key data at a glance. In: Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Accountability for the global health sector strategies 2016–2021: actions for impact. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.

33 Falla AM, Hofstraat SHI, Duffell E, Hahné SJM, Tavoschi L, Veldhuijzen IK. Hepatitis B/C in the countries of the EU/EEA: a systematic review of the prevalence among at-risk groups. *BMC Infect Dis* 2018; **18:** 79.

34 Fraser H, Martin NK, Brummer-Korvenkontio H, et al. Model projections on the impact of HCV treatment in the prevention of HCV transmission among people who inject drugs in Europe. *J Hepatol* 2018; **68:** 402–11.

35 Wiessing L, Ferri M, Grady B, et al. Hepatitis C virus infection epidemiology among people who inject drugs in Europe: a systematic review of data for scaling up treatment and prevention. *PLoS One* 2014; **9:** e103345.

36 European Centre for Disease Prevention and Control. Hepatitis B and C epidemiology in selected population groups in the EU/EAA. Sept 11, 2018. https://www.ecdc.europa.eu/en/publications-data/hepatitis-b-and-c-epidemiology-selected-population-groups-eueea (accessed Nov 4, 2021).

37 Trickey A, Fraser H, Lim AG, et al. The contribution of injection drug use to hepatitis C virus transmission globally, regionally, and at country level: a modelling study. *Lancet Gastroenterol Hepatol* 2019; **4:** 435–44.

38 WHO. Action plan for the health sector response to viral hepatitis in the WHO European Region. 2017. https://www.euro.who.int/__data/assets/pdf_file/0008/357236/Hepatitis-9789289052870-eng.pdf (accessed Nov 1, 2021).

39 Chang MH, Chen CJ, Lai MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. *N Engl J Med* 1997; **336:** 1855–59.

40 Hadler SC, Fuqiang C, Averhoff F, et al. The impact of hepatitis B vaccine in China and in the China GAVI Project. *Vaccine* 2013; **31** (suppl 9)**:** J66–72.

41 Liang X, Bi S, Yang W, et al. Epidemiological serosurvey of hepatitis B in China—declining HBV prevalence due to hepatitis B vaccination. *Vaccine* 2009; **27:** 6550–57.

42 Thomas DL. Global elimination of chronic hepatitis. *N Engl J Med* 2019; **380:** 2041–50.

43 Chang MH, You SL, Chen CJ, et al. Decreased incidence of hepatocellular carcinoma in hepatitis B vaccinees: a 20-year follow-up study. *J Natl Cancer Inst* 2009; **101:** 1348–55.

44 Lin CL, Kao JH. Review article: the prevention of hepatitis B-related hepatocellular carcinoma. *Aliment Pharmacol Ther* 2018; **48:** 5–14.

45 Blumberg BS. Hepatitis B virus, the vaccine, and the control of primary cancer of the liver. *Proc Natl Acad Sci USA* 1997; **94:** 7121–25.

46 Miglietta A, Quinten C, Lopalco PL, Duffell E. Impact of hepatitis B vaccination on acute hepatitis B epidemiology in European Union/European Economic Area countries, 2006 to 2014. *Euro Surveill* 2018; **23:** 17-00278.

47 Ahmad AA, Falla AM, Duffell E, et al. Estimating the scale of chronic hepatitis B virus infection among migrants in EU/EEA countries. *BMC Infect Dis* 2018; **18:** 34.

48 Rizzetto M, Hamid S, Negro F. The changing context of hepatitis D. *J Hepatol* 2021; **74:** 1200–11.

49 Puigvehí M, Moctezuma-Velázquez C, Villanueva A, Llovet JM. The oncogenic role of hepatitis delta virus in hepatocellular carcinoma. *JHEP Rep* 2019; **1:** 120–30.

50 Yurdaydin C, Abbas Z, Buti M, et al. Treating chronic hepatitis delta: The need for surrogate markers of treatment efficacy. *J Hepatol* 2019; **70:** 1008–15.

51 Duffell EF, Hedrich D, Mardh O, Mozalevskis A. Towards elimination of hepatitis B and C in European Union and European Economic Area countries: monitoring the World Health Organization's global health sector strategy core indicators and scaling up key interventions. *Euro Surveill* 2017; **22:** 30476.

52 Hutchinson SJ, Valerio H, McDonald SA, et al. Population impact of direct-acting antiviral treatment on new presentations of hepatitis C-related decompensated cirrhosis: a national record-linkage study. *Gut* 2020; **69:** 2223–31.

53 Belli LS, Perricone G, Adam R, et al. Impact of DAAs on liver transplantation: major effects on the evolution of indications and results. An ELITA study based on the ELTR registry. *J Hepatol* 2018; **69:** 810–17.

54 Goldberg D, Hutchinson SJ, Innes H, Dillon J. Scotland's hepatitis C action plan: achievements of the first decade and proposals for a Scottish Government Strategy (2019) for the elimination of both infection and disease. Jan 1, 2019. https://hps-beta.azurewebsites.net/web-resources-container/hepatitis-c-elimination-in-scotland (accessed Nov 2, 2021).

55 Chen Q, Ayer T, Bethea E, et al. Changes in hepatitis C burden and treatment trends in Europe during the era of direct-acting antivirals: a modelling study. *BMJ Open* 2019; **9:** e026726.

56 Izopet J, Tremeaux P, Marion O, et al. Hepatitis E virus infections in Europe. *J Clin Virol* 2019; **120:** 20–26.

57 Wang Y, Liu H, Jiang Y, Pan Q, Zhao J. Poor outcomes of acute hepatitis E in patients with cirrhotic liver diseases regardless of etiology. *Open Forum Infect Dis* 2020; **7:** ofaa107.

58 Pais R, Barritt AS 4th, Calmus Y, et al. NAFLD and liver transplantation: current burden and expected challenges. *J Hepatol* 2016; **65:** 1245–57.

59 Estes C, Anstee QM, Arias-Loste MT, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016–2030. *J Hepatol* 2018; **69:** 896–904.

60 Schattenberg JM, Lazarus JV, Newsome PN, et al. Disease burden and economic impact of diagnosed non-alcoholic steatohepatitis in five European countries in 2018: a cost-of-illness analysis. *Liver Int* 2021; **41:** 1227–42.

61 Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016; **64:** 73–84.

62 Torres DM, Williams CD, Harrison SA. Features, diagnosis, and treatment of nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2012; **10:** 837–58.

63 Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology* 2018; **67:** 123–33.

64 Younossi ZM, Blissett D, Blissett R, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. *Hepatology* 2016; **64:** 1577–86.

65 Singh S, Osna NA, Kharbanda KK. Treatment options for alcoholic and non-alcoholic fatty liver disease: a review. *World J Gastroenterol* 2017; **23:** 6549–70.

66 Dai W, Ye L, Liu A, et al. Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus: a meta-analysis. *Medicine (Baltimore)* 2017; **96:** e8179.

67 Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. *J Hepatol* 2019; **71:** 793–801.

68 Mantovani A, Petracca G, Beatrice G, et al. Non-alcoholic fatty liver disease and increased risk of incident extrahepatic cancers: a meta-analysis of observational cohort studies. *Gut* 2021; published online March 8. https://doi.org/10.1136/gutjnl-2021-324191.

69 Byrne CD, Targher G. NAFLD: a multisystem disease. *J Hepatol* 2015; **62** (suppl)**:** S47–64.

70 Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. *Nat Rev Gastroenterol Hepatol* 2013; **10:** 330–44.

71 Targher G, Tilg H, Byrne CD. Non-alcoholic fatty liver disease: a multisystem disease requiring a multidisciplinary and holistic approach. *Lancet Gastroenterol Hepatol* 2021; **6:** 578–88.

72 Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; **71:** 209–49.

73 Banales JM, Cardinale V, Carpino G, et al. Expert consensus document: cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). *Nat Rev Gastroenterol Hepatol* 2016; **13:** 261–80.

74 Spolverato G, Kim Y, Ejaz A, et al. Conditional probability of long-term survival after liver resection for intrahepatic cholangiocarcinoma: a multi-institutional analysis of 535 patients. *JAMA Surg* 2015; **150:** 538–45.

75 Huang DQ, El-Serag HB, Loomba R. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol* 2021; **18:** 223–38.

76 Stine JG, Wentworth BJ, Zimmet A, et al. Systematic review with meta-analysis: risk of hepatocellular carcinoma in non-alcoholic steatohepatitis without cirrhosis compared to other liver diseases. *Aliment Pharmacol Ther* 2018; **48:** 696–703.

77 Cucchetti A, Trevisani F, Bucci L, et al. Years of life that could be saved from prevention of hepatocellular carcinoma. *Aliment Pharmacol Ther* 2016; **43:** 814–24.

78 Park JW, Chen M, Colombo M, et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. *Liver Int* 2015; **35:** 2155–66.

79 Kudo M. Management of hepatocellular carcinoma in Japan as a world-leading model. *Liver Cancer* 2018; **7:** 134–47.

80 Bernts LHP, Jones DEJ, Kaatee MM, et al. Position statement on access to care in rare liver diseases: advancements of the European reference network (ERN) RARE-LIVER. *Orphanet J Rare Dis* 2019; **14:** 169.

81 Hirschfield GM, Karlsen TH, Lindor KD, Adams DH. Primary sclerosing cholangitis. *Lancet* 2013; **382:** 1587–99.

82 McKiernan PJ, Baker AJ, Kelly DA. The frequency and outcome of biliary atresia in the UK and Ireland. *Lancet* 2000; **355:** 25–29.

83 Davenport M, Ong E, Sharif K, et al. Biliary atresia in England and Wales: results of centralization and new benchmark. *J Pediatr Surg* 2011; **46:** 1689–94.

84 Beath S, Pearmain G, Kelly D, McMaster P, Mayer A, Buckels J. Liver transplantation in babies and children with extrahepatic biliary atresia. *J Pediatr Surg* 1993; **28:** 1044–47.

85 Beath SV, Brook GD, Kelly DA, et al. Successful liver transplantation in babies under 1 year. *BMJ* 1993; **307:** 825–28.

86 Petersen C, Harder D, Abola Z, et al. European biliary atresia registries: summary of a symposium. *Eur J Pediatr Surg* 2008; **18:** 111–16.

87 Verkade HJ, Bezerra JA, Davenport M, et al. Biliary atresia and other cholestatic childhood diseases: advances and future challenges. *J Hepatol* 2016; **65:** 631–42.

88 Rana A, Pallister Z, Halazun K, et al. Pediatric liver transplant center volume and the likelihood of transplantation. *Pediatrics* 2015; **136:** e99–107.

89 Onakpoya IJ, Heneghan CJ, Aronson JK. Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature. *BMC Med* 2016; **14:** 10.

90 US Food & Drug Administration. Drug-induced liver injury: premarketing clinical evaluation. July, 2009. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation (accessed Nov 4, 2021).

91 EMA. Non-clinical evaluation of drug-induced liver injury (DILI). July 19, 2010. https://www.ema.europa.eu/en/non-clinical-evaluation-drug-induced-liver-injury-dili (accessed Nov 4, 2021).

92 Andrade RJ, Aithal GP, Björnsson ES, et al. EASL Clinical Practice Guidelines: drug-induced liver injury. *J Hepatol* 2019; **70:** 1222–61.

93 Andrade RJ, Chalasani N, Björnsson ES, et al. Drug-induced liver injury. *Nat Rev Dis Primers* 2019; **5:** 58.

94 Sgro C, Clinard F, Ouazir K, et al. Incidence of drug-induced hepatic injuries: a French population-based study. *Hepatology* 2002; **36:** 451–55.

95 Stephens C, Robles-Diaz M, Medina-Caliz I, et al. Comprehensive analysis and insights gained from long-term experience of the Spanish DILI Registry. *J Hepatol* 2021; **75:** 86–97.

96 Wendon J, Cordoba J, Dhawan A, et al. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. *J Hepatol* 2017; **66:** 1047–81.

97 Arora M, Barquera S, Farpour Lambert NJ, et al. Stigma and obesity: the crux of the matter. *Lancet Public Health* 2019; **4:** e549–50.

98 Pranata R, Lim MA, Yonas E, et al. Body mass index and outcome in patients with COVID-19: a dose-response meta-analysis. *Diabetes Metab* 2021; **47:** 101178.

99 Kirby T. Evidence mounts on the disproportionate effect of COVID-19 on ethnic minorities. *Lancet Respir Med* 2020; **8:** 547–48.

100 Sze S, Pan D, Nevill CR, et al. Ethnicity and clinical outcomes in COVID-19: a systematic review and meta-analysis. *EClinicalMedicine* 2020; **29:** 100630.

101 EClinicalMedicine. Ethnic and racial inequity and inequality in health and science: a call for action. *EClinicalMedicine* 2021; **32:** 100782.

102 Public Health England. Beyond the data: understanding the impact of COVID-19 on BAME groups. June, 2020. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/892376/COVID_stakeholder_engagement_synthesis_beyond_the_data.pdf (accessed Nov 4, 2021).

103 Sachdeva S, Khandait H, Kopel J, Aloysius MM, Desai R, Goyal H. NAFLD and COVID-19: a pooled analysis. *SN Compr Clin Med* 2020; published online Nov 6. https://doi.org/10.1007/s42399-020-00631-3.

104 Ji D, Qin E, Xu J, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: a retrospective study. *J Hepatol* 2020; **73:** 451–53.

105 Rehm J, Shield KD. Global burden of alcohol use disorders and alcohol liver disease. *Biomedicines* 2019; **7:** E99.

106 Hart CL, Morrison DS, Batty GD, Mitchell RJ, Davey Smith G. Effect of body mass index and alcohol consumption on liver disease: analysis of data from two prospective cohort studies. *BMJ* 2010; **340:** c1240.

107 Mahli A, Hellerbrand C. Alcohol and obesity: a dangerous association for fatty liver disease. *Dig Dis* 2016; **34** (suppl 1)**:** 32–39.

108 Loomba R, Yang HI, Su J, et al. Synergism between obesity and alcohol in increasing the risk of hepatocellular carcinoma: a prospective cohort study. *Am J Epidemiol* 2013; **177:** 333–42.

109 Åberg F, Puukka P, Salomaa V, et al. Combined effects of alcohol and metabolic disorders in patients with chronic liver disease. *Clin Gastroenterol Hepatol* 2020; **18:** 995–97.

110 European Society for the Study of the Liver. HEPAHEALTH project report. September, 2018. https://easl.eu/wp-content/uploads/2018/09/EASL-HEPAHEALTH-Report.pdf (accessed Nov 4, 2021).

111 Fromme M, Schneider CV, Pereira V, et al. Hepatobiliary phenotypes of adults with alpha-1 antitrypsin deficiency. *Gut* 2021; published online Feb 25. https://doi.org/10.1136/gutjnl-2020-323729.

112 Younossi ZM, Zheng L, Stepanova M, Venkatesan C, Mir HM. Moderate, excessive or heavy alcohol consumption: each is significantly associated with increased mortality in patients with chronic hepatitis C. *Aliment Pharmacol Ther* 2013; **37:** 703–09.

113 Innes H, McDonald S, Hayes P, et al. Mortality in hepatitis C patients who achieve a sustained viral response compared to the general population. *J Hepatol* 2017; **66:** 19–27.

114 Innes HA, Hutchinson SJ, Barclay S, et al. Quantifying the fraction of cirrhosis attributable to alcohol among chronic hepatitis C virus patients: implications for treatment cost-effectiveness. *Hepatology* 2013; **57:** 451–60.

115 Akhavan Rezayat A, Dadgar Moghadam M, Ghasemi Nour M, et al. Association between smoking and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *SAGE Open Med* 2018; **6:** 2050312117745223.

116 Kim NH, Jung YS, Hong HP, et al. Association between cotinine-verified smoking status and risk of nonalcoholic fatty liver disease. *Liver Int* 2018; **38:** 1487–94.

117 Okamoto M, Miyake T, Kitai K, et al. Cigarette smoking is a risk factor for the onset of fatty liver disease in nondrinkers: a longitudinal cohort study. *PLoS One* 2018; **13:** e0195147.

118 Liu P, Xu Y, Tang Y, et al. Independent and joint effects of moderate alcohol consumption and smoking on the risks of non-alcoholic fatty liver disease in elderly Chinese men. *PLoS One* 2017; **12:** e0181497.

119 Zein CO, Unalp A, Colvin R, Liu YC, McCullough AJ. Smoking and severity of hepatic fibrosis in nonalcoholic fatty liver disease. *J Hepatol* 2011; **54:** 753–59.

120 Jung HS, Chang Y, Kwon MJ, et al. Smoking and the risk of non-alcoholic fatty liver disease: a cohort study. *Am J Gastroenterol* 2019; **114:** 453–63.

121 Björkström K, Franzén S, Eliasson B, et al. Risk factors for severe liver disease in patients with type 2 diabetes. *Clin Gastroenterol Hepatol* 2019; **17:** 2769–75.

122 Saran U, Humar B, Kolly P, Dufour JF. Hepatocellular carcinoma and lifestyles. *J Hepatol* 2016; **64:** 203–14.

123 Trichopoulos D, Bamia C, Lagiou P, et al. Hepatocellular carcinoma risk factors and disease burden in a European cohort: a nested case-control study. *J Natl Cancer Inst* 2011; **103:** 1686–95.

124 Lee YC, Cohet C, Yang YC, Stayner L, Hashibe M, Straif K. Meta-analysis of epidemiologic studies on cigarette smoking and liver cancer. *Int J Epidemiol* 2009; **38:** 1497–511.

125 Kuper H, Tzonou A, Kaklamani E, et al. Tobacco smoking, alcohol consumption and their interaction in the causation of hepatocellular carcinoma. *Int J Cancer* 2000; **85:** 498–502.

126 Moubarac JC, Parra DC, Cannon G, Monteiro CA. Food classification systems based on food processing: significance and implications for policies and actions: a systematic literature review and assessment. *Curr Obes Rep* 2014; **3:** 256–72.

127 Monteiro CA, Cannon G, Moubarac JC, Levy RB, Louzada MLC, Jaime PC. The UN Decade of Nutrition, the NOVA food classification and the trouble with ultra-processing. *Public Health Nutr* 2018; **21:** 5–17.

128 Slimani N, Deharveng G, Southgate DA, et al. Contribution of highly industrially processed foods to the nutrient intakes and patterns of middle-aged populations in the European Prospective Investigation into Cancer and Nutrition study. *Eur J Clin Nutr* 2009; **63** (suppl 4)**:** S206–25.

129 Martínez Steele E, Popkin BM, Swinburn B, Monteiro CA. The share of ultra-processed foods and the overall nutritional quality of diets in the US: evidence from a nationally representative cross-sectional study. *Popul Health Metr* 2017; **15:** 6.

130 Martínez Steele E, Baraldi LG, Louzada ML, Moubarac JC, Mozaffarian D, Monteiro CA. Ultra-processed foods and added sugars in the US diet: evidence from a nationally representative cross-sectional study. *BMJ Open* 2016; **6:** e009892.

131 Rauber F, Louzada MLDC, Martinez Steele E, et al. Ultra-processed foods and excessive free sugar intake in the UK: a nationally representative cross-sectional study. *BMJ Open* 2019; **9:** e027546.

132 Monteiro CA, Cannon G, Lawrence M, Costa Louzada ML, Pereira Machado P. Ultra-processed foods, diet quality and human health. Rome: Food and Agriculture Organization of the United Nations, 2019.

133 Mendonça RD, Lopes AC, Pimenta AM, Gea A, Martinez-Gonzalez MA, Bes-Rastrollo M. Ultra-processed food consumption and the incidence of hypertension in a Mediterranean cohort: the Seguimiento Universidad de Navarra project. *Am J Hypertens* 2017; **30:** 358–66.

134 Fiolet T, Srour B, Sellem L, et al. Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort. *BMJ* 2018; **360:** k322.

135 Lane MM, Davis JA, Beattie S, et al. Ultraprocessed food and chronic noncommunicable diseases: a systematic review and meta-analysis of 43 observational studies. *Obes Rev* 2021; **22:** e13146.

136 Srour B, Fezeu LK, Kesse-Guyot E, et al. Ultraprocessed food consumption and risk of type 2 diabetes among participants of the NutriNet-Santé prospective cohort. *JAMA Intern Med* 2020; **180:** 283–91.

137 Schnabel L, Kesse-Guyot E, Allès B, et al. Association between ultraprocessed food consumption and risk of mortality among middle-aged adults in France. *JAMA Intern Med* 2019; **179:** 490–98.

138 Hall KD, Ayuketah A, Brychta R, et al. Ultra-processed diets cause excess calorie intake and weight gain: an inpatient randomized controlled trial of ad libitum food intake. *Cell Metab* 2019; **30:** 67–77.

139 Ivancovsky-Wajcman D, Fliss-Isakov N, Webb M, et al. Ultra-processed food is associated with features of metabolic syndrome and non-alcoholic fatty liver disease. *Liver Int* 2021; **41:** 2635–45.

140 Fouad Y, Lazarus JV, Negro F, et al. MAFLD considerations as a part of the global hepatitis C elimination effort: an international perspective. *Aliment Pharmacol Ther* 2021; **53:** 1080–89.

141 Li Y, Campbell H, Kulkarni D, et al. The temporal association of introducing and lifting non-pharmaceutical interventions with the time-varying reproduction number (R) of SARS-CoV-2: a modelling study across 131 countries. *Lancet Infect Dis* 2021; **21:** 193–202.

142 Marmot M, Allen J, Goldblatt P, Herd E, Morrison J. Build back fairer: the COVID-19 Marmot review. The pandemic, socioeconomic and health inequalities in England. Dec 15, 2020. https://www.instituteofhealthequity.org/resources-reports/build-back-fairer-the-covid-19-marmot-review (accessed Nov 4, 2021).

143 Flaxman S, Mishra S, Gandy A, et al. Estimating the effects of non-pharmaceutical interventions on COVID-19 in Europe. *Nature* 2020; **584:** 257–61.

144 Davies NG, Kucharski AJ, Eggo RM, et al. Effects of non-pharmaceutical interventions on COVID-19 cases, deaths, and demand for hospital services in the UK: a modelling study. *Lancet Public Health* 2020; **5:** e375–85.

145 Nemtsov AV. Alcohol-related human losses in Russia in the 1980s and 1990s. *Addiction* 2002; **97:** 1413–25.

146 Verrill C, Markham H, Templeton A, Carr NJ, Sheron N. Alcohol-related cirrhosis—early abstinence is a key factor in prognosis, even in the most severe cases. *Addiction* 2009; **104:** 768–74.

147 WHO. Alcohol policy impact case study: the effects of alcohol control measures on mortality and life expectancy in the Russian Federation (2019). Oct 2, 2019. https://www.euro.who.int/en/publications/abstracts/alcohol-policy-impact-case-study-the-effects-of-alcohol-control-measures-on-mortality-and-life-expectancy-in-the-russian-federation-2019 (accessed Nov 4, 2021).

148 Scott N, Kuschel C, Pedrana A, et al. A model of the economic benefits of global hepatitis C elimination: an investment case. *Lancet Gastroenterol Hepatol* 2020; **5:** 940–47.

149 Palmer AY, Wade AJ, Draper B, et al. A cost-effectiveness analysis of primary versus hospital-based specialist care for direct acting antiviral hepatitis C treatment. *Int J Drug Policy* 2020; **76:** 102633.

150 Wade AJ, Doyle JS, Gane E, et al. Outcomes of treatment for hepatitis C in primary care, compared to hospital-based care: a randomized, controlled trial in people who inject drugs. *Clin Infect Dis* 2020; **70:** 1900–06.

151 Radley A, de Bruin M, Inglis SK, et al. Clinical effectiveness of pharmacist-led versus conventionally delivered antiviral treatment for hepatitis C virus in patients receiving opioid substitution therapy: a pragmatic, cluster-randomised trial. *Lancet Gastroenterol Hepatol* 2020; **5:** 809–18.

152 Oru E, Trickey A, Shirali R, Kanters S, Easterbrook P. Decentralisation, integration, and task-shifting in hepatitis C virus infection testing and treatment: a global systematic review and meta-analysis. *Lancet Glob Health* 2021; **9:** e431–45.

153 Marteau TM, Rutter H, Marmot M. Changing behaviour: an essential component of tackling health inequalities. *BMJ* 2021; **372:** n332.

154 Siegler V, Al-Hamad A, Johnson B, Wells C, Sheron N. Social inequalities in alcohol-related adult mortality by National Statistics Socio-economic Classification, England and Wales, 2001–03. *Health Stat Q* 2011; **50:** 4–39.

155 Beynon C, Hungerford D, Perkins C, et al. Burden of liver disease and inequalities in the north west of England. September, 2012. http://www.hcvaction.org.uk/sites/default/files/resources/Burden%20of%20Liver%20Disease%20in%20the%20North%20West%20of%20England%20%282012%29.pdf (accessed Nov 4, 2021).

156 Sen G, Östlin P, George A, Women and Gender Equity Knowledge Network. Unequal, unfair, ineffective and inefficient. Gender inequity in health: why it exists and how we can change it. September, 2007. https://www.who.int/social_determinants/resources/csdh_media/wgekn_final_report_07.pdf (accessed Nov 4, 2021).

157 Golovaty I, Tien PC, Price JC, Sheira L, Seligman H, Weiser SD. Food insecurity may be an independent risk factor associated with nonalcoholic fatty liver disease among low-income adults in the United States. *J Nutr* 2020; **150:** 91–98.

158 Feldstein AE, Charatcharoenwitthaya P, Treeprasertsuk S, Benson JT, Enders FB, Angulo P. The natural history of non-alcoholic fatty liver disease in children: a follow-up study for up to 20 years. *Gut* 2009; **58:** 1538–44.

159 Hagström H, Stål P, Hultcrantz R, Hemmingsson T, Andreasson A. Overweight in late adolescence predicts development of severe liver disease later in life: a 39-years follow-up study. *J Hepatol* 2016; **65:** 363–68.

160 Inchley J, Currie D, Budisavljevic S, et al. Spotlight on adolescent health and well-being. findings from the 2017/2018 Health Behaviour in School-aged Children (HBSC) survey in Europe and Canada. International report. Volume: key findings and key data. Copenhagen: WHO Regional Office for Europe; 2020.

161 Wijnhoven TM, van Raaij JM, Spinelli A, et al. WHO European Childhood Obesity Surveillance Initiative: body mass index and level of overweight among 6–9-year-old children from school year 2007/2008 to school year 2009/2010. *BMC Public Health* 2014; **14:** 806.

162 Williams J, Buoncristiano M, Nardone P, et al. A snapshot of European children's eating habits: results from the fourth round of the WHO European Childhood Obesity Surveillance Initiative (COSI). *Nutrients* 2020; **12:** E2481.

163 Howard BV, Wylie-Rosett J. Sugar and cardiovascular disease: a statement for healthcare professionals from the Committee on Nutrition of the Council on Nutrition, Physical Activity, and Metabolism of the American Heart Association. *Circulation* 2002; **106:** 523–27.

164 Harris JL, Munsell CR. Energy drinks and adolescents: what's the harm? *Nutr Rev* 2015; **73:** 247–57.

165 Johnson RK, Appel LJ, Brands M, et al. Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. *Circulation* 2009; **120:** 1011–20.

166 Muth ND, Dietz WH, Magge SN, Johnson RK. Public policies to reduce sugary drink consumption in children and adolescents. *Pediatrics* 2019; **143:** e20190282.

167 Dhingra R, Sullivan L, Jacques PF, et al. Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. *Circulation* 2007; **116:** 480–88.

168 Geidl-Flueck B, Hochuli M, Németh Á, et al. Fructose- and sucrose- but not glucose-sweetened beverages promote hepatic de novo lipogenesis: a randomized controlled trial. *J Hepatol* 2021; **75:** 46–54.

169 Geurtsen ML, Santos S, Gaillard R, Felix JF, Jaddoe VWV. Associations between intake of sugar-containing beverages in infancy with liver fat accumulation at school age. *Hepatology* 2021; **73:** 560–70.

170 Ayala-Marín AM, Iguacel I, Miguel-Etayo P, Moreno LA. Consideration of social disadvantages for understanding and preventing obesity in children. *Front Public Health* 2020; **8:** 423.

171 Popkin BM, Ng SW. Sugar-sweetened beverage taxes: lessons to date and the future of taxation. *PLoS Med* 2021; **18:** e1003412.

172 Adams J, Mytton O, White M, Monsivais P. Why are some population interventions for diet and obesity more equitable and effective than others? The role of individual agency. *PLoS Med* 2016; **13:** e1001990.

173 Douglass CH, Pedrana A, Lazarus JV, et al. Pathways to ensure universal and affordable access to hepatitis C treatment. *BMC Med* 2018; **16:** 175.

174 Garcia A, Moore Boffi S, Gayet-Ageron A, Vernaz N. Access to unauthorized hepatitis C generics: perception and knowledge of physicians, pharmacists, patients and non-healthcare professionals. *PLoS One* 2019; **14:** e0223649.

175 Bonetti A, Giuliani J. Implications of drugs with rebate in Europe. *Lancet Reg Health Eur* 2021; **3:** 100060.

176 European Commission. COVID-19's impact on migrant communities. June 16, 2020. https://ec.europa.eu/migrant-integration/news/covid-19s-impact-on-migrant-communities (accessed Nov 4, 2021).

177 Kluge HHP, Jakab Z, Bartovic J, D'Anna V, Severoni S. Refugee and migrant health in the COVID-19 response. *Lancet* 2020; **395:** 1237–39.

178 Huizar MI, Arena R, Laddu DR. The global food syndemic: the impact of food insecurity, malnutrition and obesity on the healthspan amid the COVID-19 pandemic. *Prog Cardiovasc Dis* 2021; **64:** 105–07.

179 UNICEF, WHO, International Federation of Red Cross and Red Crescent Societies. Social stigma associated with the coronavirus disease (COVID-19). Feb 24, 2020. https://www.unicef.org/documents/social-stigma-associated-coronavirus-disease-covid-19 (accessed Nov 4, 2021).

180 Bagcchi S. Stigma during the COVID-19 pandemic. *Lancet Infect Dis* 2020; **20:** 782.

181 Chandrashekhar V. The burden of stigma. *Science* 2020; **369:** 1419–23.

182 Pellegrini M, Ponzo V, Rosato R, et al. Changes in weight and nutritional habits in adults with obesity during the "lockdown" period caused by the COVID-19 virus emergency. *Nutrients* 2020; **12:** E2016.

183 Tan M, He FJ, MacGregor GA. Obesity and covid-19: the role of the food industry. *BMJ* 2020; **369:** m2237.

184 Simões D, Stengaard AR, Combs L, Raben D. Impact of the COVID-19 pandemic on testing services for HIV, viral hepatitis and sexually transmitted infections in the WHO European Region, March to August 2020. *Euro Surveill* 2020; **25:** 2001943.

185 Blach S, Kondili LA, Aghemo A, et al. Impact of COVID-19 on global HCV elimination efforts. *J Hepatol* 2021; **74:** 31–36.

186 Kondili LA, Marcellusi A, Ryder S, Craxì A. Will the COVID-19 pandemic affect HCV disease burden? *Dig Liver Dis* 2020; **52:** 947–49.

187 Cox AL, El-Sayed MH, Kao JH, et al. Progress towards elimination goals for viral hepatitis. *Nat Rev Gastroenterol Hepatol* 2020; **17:** 533–42.

188 Hermetet C, Dubois F, Gaudy-Graffin C, et al. Continuum of hepatitis C care in France: a 20-year cohort study. *PLoS One* 2017; **12:** e0183232.

189 Brouard C, Pillonel J, Boussac M, et al. French hepatitis C care cascade: substantial impact of direct-acting antivirals, but the road to elimination is still long. *BMC Infect Dis* 2020; **20:** 759.

190 European Centre for Disease Control and Prevention. Hepatitis B and C testing activities, needs, and priorities in the EU/EEA. May, 2017. https://www.ecdc.europa.eu/sites/default/files/documents/HepatitisBC-testing-in-EU-May2017.pdf (accessed Nov 1, 2021).

191 Sinn DH, Kang D, Kang M, et al. Late presentation of hepatitis B among patients with newly diagnosed hepatocellular carcinoma: a national cohort study. *BMC Cancer* 2019; **19:** 286.

192 Alexander GC, Stoller KB, Haffajee RL, Saloner B. An epidemic in the midst of a pandemic: opioid use disorder and COVID-19. *Ann Intern Med* 2020; **173:** 57–58.

193 Schlosser A, Harris S. Care during COVID-19: drug use, harm reduction, and intimacy during a global pandemic. *Int J Drug Policy* 2020; **83:** 102896.

194 National Harm Reduction Coalition. COVID-19 guidance for people who use drugs and harm reduction programs. March 11, 2020. https://harmreduction.org/blog/covid-19-guidance-for-people-who-use-drugs-and-harm-reduction-programs/ (accessed Nov 4, 2021).

195 Public Health England. Alcohol consumption and harm during the COVID-19 pandemic. July 15, 2021. https://www.gov.uk/government/publications/alcohol-consumption-and-harm-during-the-covid-19-pandemic (accessed Nov 4, 2021).

196 Public Health England. Wider impacts of COVID-19 on health monitoring tool. July 16, 2020. https://www.gov.uk/government/statistics/wider-impacts-of-covid-19-on-health-monitoring-tool (accessed Nov 1, 2021).

197 Cook JE, Purdie-Vaughns V, Meyer IH, Busch JTA. Intervening within and across levels: a multilevel approach to stigma and public health. *Soc Sci Med* 2014; **103:** 101–09.

198 Hatzenbuehler ML, Phelan JC, Link BG. Stigma as a fundamental cause of population health inequalities. *Am J Public Health* 2013; **103:** 813–21.

199 Nyblade L, Stockton MA, Giger K, et al. Stigma in health facilities: why it matters and how we can change it. *BMC Med* 2019; **17:** 25.

200 Marshall AD, Cunningham EB, Nielsen S, et al. Restrictions for reimbursement of interferon-free direct-acting antiviral drugs for HCV infection in Europe. *Lancet Gastroenterol Hepatol* 2018; **3:** 125–33.

201 Rigas G, Williams K, Sumithran P, et al. Delays in healthcare consultations about obesity—barriers and implications. *Obes Res Clin Pract* 2020; **14:** 487–90.

202 Biancarelli DL, Biello KB, Childs E, et al. Strategies used by people who inject drugs to avoid stigma in healthcare settings. *Drug Alcohol Depend* 2019; **198:** 80–86.

203 Pascoe EA, Smart Richman L. Perceived discrimination and health: a meta-analytic review. *Psychol Bull* 2009; **135:** 531–54.

204 Committee on the Science of Changing Behavioral Health Social Norms, Board on Behavioral, Cognitive, and Sensory Sciences, Division of Behavioral and Social Sciences and Education, National Academies of Sciences, Engineering, and Medicine. Ending discrimination against people with mental and substance use disorders: the evidence for stigma change. Washington, DC: National Academies Press, 2016.

205 Puhl R, Suh Y. Health consequences of weight stigma: implications for obesity prevention and treatment. *Curr Obes Rep* 2015; **4:** 182–90.

206 Hall W, Carter A, Forlini C. The brain disease model of addiction: is it supported by the evidence and has it delivered on its promises? *Lancet Psychiatry* 2015; **2:** 105–10.

207 Trujols J. The brain disease model of addiction: challenging or reinforcing stigma? *Lancet Psychiatry* 2015; **2:** 292.

208 Corrigan PW, Morris SB, Michaels PJ, Rafacz JD, Rüsch N. Challenging the public stigma of mental illness: a meta-analysis of outcome studies. *Psychiatr Serv* 2012; **63:** 963–73.

209 Thornicroft G, Rose D, Kassam A, Sartorius N. Stigma: ignorance, prejudice or discrimination? *Br J Psychiatry* 2007; **190:** 192–93.

210 Szeto A, Dobson KS, Luong D, Krupa T, Kirsh B. Workplace antistigma programs at the Mental Health Commission of Canada: part 1. Processes and projects. *Can J Psychiatry* 2019; **64** (suppl)**:** 5S–12S.

211 Henderson C, Noblett J, Parke H, et al. Mental health-related stigma in health care and mental health-care settings. *Lancet Psychiatry* 2014; **1:** 467–82.

212 Knaak S, Modgill G, Patten SB. Key ingredients of anti-stigma programs for health care providers: a data synthesis of evaluative studies. *Can J Psychiatry* 2014; **59** (suppl 1)**:** S19–26.

213 Rojas Rojas T, Di Beo V, Delorme J, et al. Lower HCV treatment uptake in women who have received opioid agonist therapy before and during the DAA era: the ANRS FANTASIO project. *Int J Drug Policy* 2019; **72:** 61–68.

214 Durand F. The quest for equity in liver transplantation: another lesson learned from women. *J Hepatol* 2011; **54:** 401–02.

215 Myers RP, Shaheen AA, Aspinall AI, Quinn RR, Burak KW. Gender, renal function, and outcomes on the liver transplant waiting list: assessment of revised MELD including estimated glomerular filtration rate. *J Hepatol* 2011; **54:** 462–70.

216 Cholongitas E, Marelli L, Kerry A, et al. Female liver transplant recipients with the same GFR as male recipients have lower MELD scores—a systematic bias. *Am J Transplant* 2007; **7:** 685–92.

217 Dutton GR, Lewis TT, Durant N, et al. Perceived weight discrimination in the CARDIA study: differences by race, sex, and weight status. *Obesity (Silver Spring)* 2014; **22:** 530–36.

218 Spahlholz J, Baer N, König HH, Riedel-Heller SG, Luck-Sikorski C. Obesity and discrimination—a systematic review and meta-analysis of observational studies. *Obes Rev* 2016; **17:** 43–55.

219 Udo T, Purcell K, Grilo CM. Perceived weight discrimination and chronic medical conditions in adults with overweight and obesity. *Int J Clin Pract* 2016; **70:** 1003–11.

220 Phelan SM, Burgess DJ, Yeazel MW, Hellerstedt WL, Griffin JM, van Ryn M. Impact of weight bias and stigma on quality of care and outcomes for patients with obesity. *Obes Rev* 2015; **16:** 319–26.

221 Organisation for Economic Co-operation and Development. The heavy burden of obesity: the economics of prevention. Oct 10, 2019. https://www.oecd.org/health/the-heavy-burden-of-obesity-67450d67-en.htm (accessed Nov 4, 2021).

222 Barry CL, Gollust SE, McGinty EE, Niederdeppe J. Effects of messages from a media campaign to increase public awareness of childhood obesity. *Obesity (Silver Spring)* 2014; **22:** 466–73.

223 Brewis A, SturtzSreetharan C, Wutich A. Obesity stigma as a globalizing health challenge. *Global Health* 2018; **14:** 20.

224 Fruh SM, Nadglowski J, Hall HR, Davis SL, Crook ED, Zlomke K. Obesity stigma and bias. *J Nurse Pract* 2016; **12:** 425–32.

225 Tomiyama AJ, Carr D, Granberg EM, et al. How and why weight stigma drives the obesity 'epidemic' and harms health. *BMC Med* 2018; **16:** 123.

226 Hirschfeld-Dicker L, Samuel RD, Tiram Vakrat E, Dubnov-Raz G. Preferred weight-related terminology by parents of children with obesity. *Acta Paediatr* 2019; **108:** 712–17.

227 Himmelstein MS, Puhl RM. Weight-based victimization from friends and family: implications for how adolescents cope with weight stigma. *Pediatr Obes* 2019; **14:** e12453.

228 Bischof GN, Park DC. Obesity and aging: consequences for cognition, brain structure, and brain function. *Psychosom Med* 2015; **77:** 697–709.

229 Morsiani C, Bacalini MG, Santoro A, et al. The peculiar aging of human liver: a geroscience perspective within transplant context. *Ageing Res Rev* 2019; **51:** 24–34.

230 Saif-Ur-Rahman KM, Mamun R, Eriksson E, He Y, Hirakawa Y. Discrimination against the elderly in health-care services: a systematic review. *Psychogeriatrics* 2021; **21:** 418–29.

231 Chang ES, Kannoth S, Levy S, Wang SY, Lee JE, Levy BR. Global reach of ageism on older persons' health: a systematic review. *PLoS One* 2020; **15:** e0220857.

232 van den Heuvel WJ, van Santvoort MM. Experienced discrimination amongst European old citizens. *Eur J Ageing* 2011; **8:** 291–99.

233 Burnes D, Sheppard C, Henderson CR Jr, et al. Interventions to reduce ageism against older adults: a systematic review and meta-analysis. *Am J Public Health* 2019; **109:** e1–9.

234 Wakeman SE. Language and addiction: choosing words wisely. *Am J Public Health* 2013; **103:** e1–2.

235 Broyles LM, Binswanger IA, Jenkins JA, et al. Confronting inadvertent stigma and pejorative language in addiction scholarship: a recognition and response. *Subst Abus* 2014; **35:** 217–21.

236 Kyle TK, Puhl RM. Putting people first in obesity. *Obesity (Silver Spring)* 2014; **22:** 1211.

237 Beuers U, Gershwin ME, Gish RG, et al. Changing nomenclature for PBC: from 'cirrhosis' to 'cholangitis'. *J Hepatol* 2015; **63:** 1285–87.

238 Thursz M, Gual A, Lackner C, et al. EASL Clinical Practice Guidelines: management of alcohol-related liver disease. *J Hepatol* 2018; **69:** 154–81.

239 Eslam M, Sanyal AJ, George J, et al. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. *Gastroenterology* 2020; **158:** 1999–2014.

240 Fouad Y, Elwakil R, Elsahhar M, et al. The NAFLD-MAFLD debate: eminence *vs* evidence. *Liver Int* 2021; **41:** 255–60.

241 Tilg H, Effenberger M. From NAFLD to MAFLD: when pathophysiology succeeds. *Nat Rev Gastroenterol Hepatol* 2020; **17:** 387–88.

242 Clayton M, Fabrellas N, Luo J, et al. From NAFLD to MAFLD: nurse and allied health perspective. *Liver Int* 2021; **41:** 683–91.

243 Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. *J Hepatol* 2020; **73:** 202–09.

244 Shiha G, Korenjak M, Eskridge W, et al. Redefining fatty liver disease: an international patient perspective. *Lancet Gastroenterol Hepatol* 2021; **6:** 73–79.

245 Lazarus JV, Kakalou C, Palayew A, et al. A Twitter discourse analysis of negative feelings and stigma related to NAFLD, NASH and obesity. *Liver Int* 2021; **41:** 2295–307.

246 Méndez-Sánchez N, Díaz-Orozco L, Córdova-Gallardo J. Redefinition of fatty liver disease from NAFLD to MAFLD raised disease awareness: Mexican experience. *J Hepatol* 2021; **75:** 221–22.

247 Fouad Y, Gomaa A, Semida N, Ghany WA, Attia D. Change from NAFLD to MAFLD increases the awareness of fatty liver disease in primary care physicians and specialists. *J Hepatol* 2021; **74:** 1254–56.

248 Hydes T, Moore M, Stuart B, et al. Can routine blood tests be modelled to detect advanced liver disease in the community: model derivation and validation using UK primary and secondary care data. *BMJ Open* 2021; **11:** e044952.

249 Ginès P, Graupera I, Lammert F, et al. Screening for liver fibrosis in the general population: a call for action. *Lancet Gastroenterol Hepatol* 2016; **1:** 256–60.

250 Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. *Lancet* 2017; **389:** 2239–51.

251 Younossi ZM, Ong JP, Takahashi H, et al. A global survey of physicians' knowledge about non-alcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2021; published online July 3. https://doi.org/10.1016/j.cgh.2021.06.048.

252 Anastasaki M, Papadakis S, Linardakis M, Anyfantakis D, Symvoulakis EK, Lionis C. Burden of metabolic syndrome among primary care patients in Crete, Greece: a descriptive study. *Eur J Gen Pract* 2020; **26:** 166–74.

253 Reimer KC, Wree A, Roderburg C, Tacke F. New drugs for NAFLD: lessons from basic models to the clinic. *Hepatol Int* 2020; **14:** 8–23.

254 Jepsen P, Ott P, Andersen PK, Sørensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. *Hepatology* 2010; **51:** 1675–82.

255 Innes H, Morling JR, Aspinall EA, Goldberg DJ, Hutchinson SJ, Guha IN. Late diagnosis of chronic liver disease in a community cohort (UK Biobank): determinants and impact on subsequent survival. *Public Health* 2020; **187:** 165–71.

256 Shah ND, Ventura-Cots M, Abraldes JG, et al. Alcohol-related liver disease is rarely detected at early stages compared with liver diseases of other etiologies worldwide. *Clin Gastroenterol Hepatol* 2019; **17:** 2320–29.

257 Forner A, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet* 2018; **391:** 1301–14.

258 Suijkerbuijk AWM, van Hoek AJ, Koopsen J, et al. Cost-effectiveness of screening for chronic hepatitis B and C among migrant populations in a low endemic country. *PLoS One* 2018; **13:** e0207037.

259 European Centre for Disease Control and Prevention. Public health guidance on screening and vaccination for infectious diseases in newly arrived migrants within the EU/EEA. November, 2018. https://www.ecdc.europa.eu/en/publications-data/public-health-guidance-screening-and-vaccination-infectious-diseases-newly (accessed Nov 1, 2021).

260 Jakab SS, Garcia-Tsao G. Screening and surveillance of varices in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2019; **17:** 26–29.

261 Newsome PN, Cramb R, Davison SM, et al. Guidelines on the management of abnormal liver blood tests. *Gut* 2018; **67:** 6–19.

262 El-Gohary M, Moore M, Roderick P, et al. Local care and treatment of liver disease (LOCATE)—a cluster-randomized feasibility study to discover, assess and manage early liver disease in primary care. *PLoS One* 2018; **13:** e0208798.

263 Harman DJ, Ryder SD, James MW, et al. Direct targeting of risk factors significantly increases the detection of liver cirrhosis in primary care: a cross-sectional diagnostic study utilising transient elastography. *BMJ Open* 2015; **5:** e007516.

264 Castera L. Screening for liver fibrosis in primary care: focus on subjects above 40 and with metabolic risk factors. *United European Gastroenterol J* 2021; **9:** 889–91.

265 Caballería L, Pera G, Arteaga I, et al. High prevalence of liver fibrosis among European adults with unknown liver disease: a population-based study. *Clin Gastroenterol Hepatol* 2018; **16:** 1138–45.

266 Kelly ML, Riordan SM, Bopage R, Lloyd AR, Post JJ. Capacity of non-invasive hepatic fibrosis algorithms to replace transient elastography to exclude cirrhosis in people with hepatitis C virus infection: a multi-centre observational study. *PLoS One* 2018; **13:** e0192763.

267 Anderson P, Bendtsen P, Spak F, et al. Improving the delivery of brief interventions for heavy drinking in primary health care: outcome results of the Optimizing Delivery of Health Care Intervention (ODHIN) five-country cluster randomized factorial trial. *Addiction* 2016; **111:** 1935–45.

268 Parkes J, Guha IN, Harris S, Rosenberg WM, Roderick PJ. Systematic review of the diagnostic performance of serum markers of liver fibrosis in alcoholic liver disease. *Comp Hepatol* 2012; **11:** 5.

269 Guha IN, Parkes J, Roderick PR, Harris S, Rosenberg WM. Non-invasive markers associated with liver fibrosis in non-alcoholic fatty liver disease. *Gut* 2006; **55:** 1650–60.

270 European Association for Study of Liver. EASL-ALEH Clinical Practice Guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. *J Hepatol* 2015; **63:** 237–64.

271 Dietrich CF, Bamber J, Berzigotti A, et al. EFSUMB guidelines and recommendations on the clinical use of liver ultrasound elastography, update 2017 (long version). *Ultraschall Med* 2017; **38:** e16–47.

272 Szakács Z, Erőss B, Soós A, et al. Baveno criteria safely identify patients with compensated advanced chronic liver disease who can avoid variceal screening endoscopy: a diagnostic test accuracy meta-analysis. *Front Physiol* 2019; **10:** 1028.

273 Qi X, Berzigotti A, Cardenas A, Sarin SK. Emerging non-invasive approaches for diagnosis and monitoring of portal hypertension. *Lancet Gastroenterol Hepatol* 2018; **3:** 708–19.

274 Harris R, Harman DJ, Card TR, Aithal GP, Guha IN. Prevalence of clinically significant liver disease within the general population, as defined by non-invasive markers of liver fibrosis: a systematic review. *Lancet Gastroenterol Hepatol* 2017; **2:** 288–97.

275 Sylvester R, Hydes TJ, Hales A, Williams R, Sheron N. Validation of the liver traffic light test as a predictive model for survival and development of liver-related events. *JGH Open* 2021; **5:** 549–57.

276 Tanajewski L, Harris R, Harman DJ, et al. Economic evaluation of a community-based diagnostic pathway to stratify adults for non-alcoholic fatty liver disease: a Markov model informed by a feasibility study. *BMJ Open* 2017; **7:** e015659.

277 Serra-Burriel M, Graupera I, Torán P, et al. Transient elastography for screening of liver fibrosis: cost-effectiveness analysis from six prospective cohorts in Europe and Asia. *J Hepatol* 2019; **71:** 1141–51.

278 Harrison P, Hogan BJ, Floros L, Davies E. Assessment and management of cirrhosis in people older than 16 years: summary of NICE guidance. *BMJ* 2016; **354:** i2850.

279 Byrne CD, Patel J, Scorletti E, Targher G. Tests for diagnosing and monitoring non-alcoholic fatty liver disease in adults. *BMJ* 2018; **362:** k2734.

280 Wai C-T, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* 2003; **38:** 518–26.

281 Forns X, Ampurdanès S, Llovet JM, et al. Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. *Hepatology* 2002; **36:** 986–92.

282 Thiele M, Madsen BS, Hansen JF, Detlefsen S, Antonsen S, Krag A. Accuracy of the enhanced liver fibrosis test *vs* fibrotest, elastography, and indirect markers in detection of advanced fibrosis in patients with alcoholic liver disease. *Gastroenterology* 2018; **154:** 1369–79.

283 Srivastava A, Gailer R, Tanwar S, et al. Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease. *J Hepatol* 2019; **71:** 371–78.

284 Caballeria L, Augustin S, Broquetas T, et al. Recommendations for the detection, diagnosis and follow-up of patients with non-alcoholic fatty liver disease in primary and hospital care. *Med Clin (Barc)* 2019; **153:** 169–77.

285 Yki-Järvinen H, Arkkila P, Eskelinen S, et al. Non-alcoholic fatty liver disease (NAFLD). Jan 8, 2020. https://www.kaypahoito.fi/en/ccs00129 (accessed Nov 4, 2021).

286 McCarthy M. Sustainable general practice: looking across Europe. *Br J Gen Pract* 2016; **66:** 36.

287 Grattagliano I, D'Ambrosio G, Palmieri VO, Moschetta A, Palasciano G, Portincasa P. Improving nonalcoholic fatty liver disease management by general practitioners: a critical evaluation and impact of an educational training program. *J Gastrointestin Liver Dis* 2008; **17:** 389–94.

288 Costa M, Yaya I, Mora M, et al. Barriers and levers in screening and care for alcohol use disorders among French general practitioners: results from a computer-assisted telephone interview-based survey. *Alcohol Treat Q* 2019; **37:** 207–24.

289 Loguercio C, Tiso A, Cotticelli G, et al. Management of chronic liver disease by general practitioners in southern Italy: unmet educational needs. *Dig Liver Dis* 2011; **43:** 736–41.

290 Galle PR, Forner A, Llovet JM, et al. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018; **69:** 182–236.

291 Tzartzeva K, Obi J, Rich NE, et al. Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis: a meta-analysis. *Gastroenterology* 2018; **154:** 1706–18.

292 Johnson P, Berhane S, Kagebayashi C, et al. Impact of disease stage and aetiology on survival in hepatocellular carcinoma: implications for surveillance. *Br J Cancer* 2017; **116:** 441–47.

293 Cucchetti A, Trevisani F, Pecorelli A, et al. Estimation of lead-time bias and its impact on the outcome of surveillance for the early diagnosis of hepatocellular carcinoma. *J Hepatol* 2014; **61:** 333–41.

294 Zhao C, Jin M, Le RH, et al. Poor adherence to hepatocellular carcinoma surveillance: a systematic review and meta-analysis of a complex issue. *Liver Int* 2018; **38:** 503–14.

295 WHO. Innovative care for chronic conditions: building blocks for action. 2002. https://apps.who.int/iris/handle/10665/42500 (accessed Nov 4, 2021).
296 Eaton S, Roberts S, Turner B. Delivering person centred care in long term conditions. *BMJ* 2015; **350:** h181.
297 Brinkmann-Sass C, Richter L, Silberzahn T, Somauroo A. The European path to reimbursement for digital health solutions. Sept 17, 2020. https://www.mckinsey.com/industries/life-sciences/our-insights/the-european-path-to-reimbursement-for-digital-health-solutions (accessed Nov 4, 2021).
298 Salisbury C, Man MS, Bower P, et al. Management of multimorbidity using a patient-centred care model: a pragmatic cluster-randomised trial of the 3D approach. *Lancet* 2018; **392:** 41–50.
299 Centis E, Marzocchi R, Di Domizio S, Ciaravella MF, Marchesini G. The effect of lifestyle changes in non-alcoholic fatty liver disease. *Dig Dis* 2010; **28:** 267–73.
300 Tilg H, Moschen A. Weight loss: cornerstone in the treatment of non-alcoholic fatty liver disease. *Minerva Gastroenterol Dietol* 2010; **56:** 159–67.
301 Trooskin SB, Poceta J, Towey CM, et al. Results from a geographically focused, community-based HCV screening, linkage-to-care and patient navigation program. *J Gen Intern Med* 2015; **30:** 950–57.
302 Ford MM, Jordan AE, Johnson N, et al. Check hep C: a community-based approach to hepatitis C diagnosis and linkage to care in high-risk populations. *J Public Health Manag Pract* 2018; **24:** 41–48.
303 Public Health England. Atlas of variation. 2020. https://fingertips.phe.org.uk/profile/atlas-of-variation (accessed Nov 4, 2021).
304 Younossi ZM, Marchesini G, Pinto-Cortez H, Petta S. Epidemiology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: implications for liver transplantation. *Transplantation* 2019; **103:** 22–27.
305 Lilford RJ, Bentham L, Girling A, et al. Birmingham and Lambeth Liver Evaluation Testing Strategies (BALLETS): a prospective cohort study. *Health Technol Assess* 2013; **17:** i–xiv, 1–307.
306 Grover A, Joshi A. An overview of chronic disease models: a systematic literature review. *Glob J Health Sci* 2014; **7:** 210–27.
307 Stellefson M, Dipnarine K, Stopka C. The chronic care model and diabetes management in US primary care settings: a systematic review. *Prev Chronic Dis* 2013; **10:** E26.
308 Yeoh EK, Wong MCS, Wong ELY, et al. Benefits and limitations of implementing Chronic Care Model (CCM) in primary care programs: a systematic review. *Int J Cardiol* 2018; **258:** 279–88.
309 NCD Countdown 2030 collaborators. NCD Countdown 2030: pathways to achieving Sustainable Development Goal target 3.4. *Lancet* 2020; **396:** 918–34.
310 Chan JCN, Lim LL, Wareham NJ, et al. The *Lancet* Commission on diabetes: using data to transform diabetes care and patient lives. *Lancet* 2021; **396:** 2019–82.
311 Afshin A, Forouzanfar MH, Reitsma MB, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med* 2017; **377:** 13–27.
312 Morando F, Maresio G, Piano S, et al. How to improve care in outpatients with cirrhosis and ascites: a new model of care coordination by consultant hepatologists. *J Hepatol* 2013; **59:** 257–64.
313 Wang Q, Davis PB, Xu R. COVID-19 risk, disparities and outcomes in patients with chronic liver disease in the United States. *EClinicalMedicine* 2021; **31:** 100688.
314 Royal College of Nursing. Caring for people with liver disease including liver transplantation: a competence framework for nursing. Sept 18, 2019. https://www.rcn.org.uk/professional-development/publications/pub-007733 (accessed June 15, 2021).
315 LIVERHOPE. LIVERHOPE project. 2017. https://www.liverhope-h2020.eu/index_en (accessed June 15, 2021).
316 Fabrellas N, Carol M, Palacio E, et al. Nursing care of patients with cirrhosis: the LiverHope nursing project. *Hepatology* 2020; **71:** 1106–16.
317 Ginés P, Quintero E, Arroyo V, et al. Compensated cirrhosis: natural history and prognostic factors. *Hepatology* 1987; **7:** 122–28.
318 Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. *Lancet* 2014; **383:** 1749–61.
319 Sepanlou SG, Safiri S, Bisignano C, et al. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol* 2020; **5:** 245–66.
320 Blachier M, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. *J Hepatol* 2013; **58:** 593–608.
321 Standing H, Jarvis H, Orr J, et al. How can primary care enhance end-of-life care for liver disease? Qualitative study of general practitioners' perceptions and experiences. *BMJ Open* 2017; **7:** e017106.
322 Hull SA, Rajabzadeh V, Thomas N, et al. Improving coding and primary care management for patients with chronic kidney disease: an observational controlled study in East London. *Br J Gen Pract* 2019; **69:** e454–61.
323 Costa M, Barré T, Coste M, et al. Screening and care for alcohol use disorder in France: expectations, barriers and levers using a mixed-methods approach. *BMC Public Health* 2020; **20:** 358.
324 Standing HC, Jarvis H, Orr J, et al. GPs' experiences and perceptions of early detection of liver disease: a qualitative study in primary care. *Br J Gen Pract* 2018; **68:** e743–49.
325 Low JTS, Rohde G, Pittordou K, et al. Supportive and palliative care in people with cirrhosis: international systematic review of the perspective of patients, family members and health professionals. *J Hepatol* 2018; **69:** 1260–73.
326 National Institute for Health and Care Excellence. End of life care for adults: service delivery. Oct 16, 2019. https://www.nice.org.uk/guidance/ng142 (accessed Nov 4, 2021).
327 National Institute for Health and Care Excellence. Care of dying adults in the last days of life. Dec 16, 2015. https://www.nice.org.uk/guidance/ng31 (accessed Nov 4, 2021).
328 German Guideline Program in Oncology. Evidence-based guideline: palliative care for patients with incurable cancer. May, 2015. https://www.leitlinienprogramm-onkologie.de/fileadmin/_migrated/content_uploads/Guideline_Palliative_Care_Short_Version_01.pdf (accessed Nov 4, 2021).
329 Miquel M, Clèries M, Vergara M, Vela E. Economic burden of cirrhosis in Catalonia: a population-based analysis. *BMJ Open* 2018; **8:** e018012.
330 Marinho RT, Duarte H, Gíria J, Nunes J, Ferreira A, Velosa J. The burden of alcoholism in fifteen years of cirrhosis hospital admissions in Portugal. *Liver Int* 2015; **35:** 746–55.
331 Heydtmann M, McDonald SA. Survival and re-admission of patients admitted with alcoholic liver disease to a West of Scotland hospital. *Scott Med J* 2013; **58:** 134–38.
332 Jepsen P, Vilstrup H, Sørensen HT. Alcoholic cirrhosis in Denmark—population-based incidence, prevalence, and hospitalization rates between 1988 and 2005: a descriptive cohort study. *BMC Gastroenterol* 2008; **8:** 3.
333 Hartley JL, Davenport M, Kelly DA. Biliary atresia. *Lancet* 2009; **374:** 1704–13.
334 Wong EL, Cheung AW, Leung MC, et al. Unplanned readmission rates, length of hospital stay, mortality, and medical costs of ten common medical conditions: a retrospective analysis of Hong Kong hospital data. *BMC Health Serv Res* 2011; **11:** 149.
335 Graupera I, Solà E, Fabrellas N, et al. Urine monocyte chemoattractant protein-1 is an independent predictive factor of hospital readmission and survival in cirrhosis. *PLoS One* 2016; **11:** e0157371.
336 Piano S, Morando F, Carretta G, et al. Predictors of early readmission in patients with cirrhosis after the resolution of bacterial infections. *Am J Gastroenterol* 2017; **112:** 1575–83.
337 Hudson B, Round J, Georgeson B, et al. Cirrhosis with ascites in the last year of life: a nationwide analysis of factors shaping costs, health-care use, and place of death in England. *Lancet Gastroenterol Hepatol* 2018; **3:** 95–103.
338 Tapper EB, Finkelstein D, Mittleman MA, Piatkowski G, Chang M, Lai M. A quality improvement initiative reduces 30-day rate of readmission for patients with cirrhosis. *Clin Gastroenterol Hepatol* 2016; **14:** 753–59.
339 Kole AA, le Cam Y. The added value of centres of expertise for rare disease patients in Europe. *Orphanet J Rare Dis* 2010; **5:** O4.

340 Syed AM, Camp R, Mischorr-Boch C, Houÿez F, Aro AR. Policy recommendations for rare disease centres of expertise. *Eval Program Plann* 2015; **52:** 78–84.

341 Gauthier F, Luciani JL, Chardot C, et al. Determinants of life span after Kasai operation at the era of liver transplantation. *Tohoku J Exp Med* 1997; **181:** 97–107.

342 Serinet MO, Broué P, Jacquemin E, et al. Management of patients with biliary atresia in France: results of a decentralized policy 1986–2002. *Hepatology* 2006; **44:** 75–84.

343 Tumiene B, Graessner H. Rare disease care pathways in the EU: from odysseys and labyrinths towards highways. *J Community Genet* 2021; **12:** 231–39.

344 Boettler T, Newsome PN, Mondelli MU, et al. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. *JHEP Rep* 2020; **2:** 100113.

345 Serper M, Cubell AW, Deleener ME, et al. Telemedicine in liver disease and beyond: can the COVID-19 crisis lead to action? *Hepatology* 2020; **72:** 723–28.

346 National Health Service. Advice and guidance. 2021. https://www.england.nhs.uk/elective-care-transformation/best-practice-solutions/advice-and-guidance/ (accessed Nov 4, 2021).

347 Richman LS, Lattanner MR. Self-regulatory processes underlying structural stigma and health. *Soc Sci Med* 2014; **103:** 94–100.

348 WHO. Report of the Commission on Ending Childhood Obesity. 2016. https://apps.who.int/iris/bitstream/handle/10665/204176/9789241510066_eng.pdf (accessed Nov 4, 2021).

349 Corrigan PW, Larson JE, Rüsch N. Self-stigma and the "why try" effect: impact on life goals and evidence-based practices. *World Psychiatry* 2009; **8:** 75–81.

350 Dietz WH, Baur LA, Hall K, et al. Management of obesity: improvement of health-care training and systems for prevention and care. *Lancet* 2015; **385:** 2521–33.

351 Stagg HR, Surey J, Francis M, et al. Improving engagement with healthcare in hepatitis C: a randomised controlled trial of a peer support intervention. *BMC Med* 2019; **17:** 71.

352 Ursic-Bedoya J, Dumortier J, Altwegg R, et al. Alcohol consumption the day of liver transplantation for alcohol-associated liver disease does not affect long-term survival: a case-control study. *Liver Transpl* 2021; **27:** 34–42.

353 Plank LD, Russell K. Nutrition in liver transplantation: too little or too much? *Curr Opin Clin Nutr Metab Care* 2015; **18:** 501–07.

354 WHO. ICD-11 for mortality and morbidity statistics (ICD-11 MMS). May, 2021. https://icd.who.int/browse11/l-m/en (accessed Nov 4, 2021).

355 Anderson P, de Bruijn A, Angus K, Gordon R, Hastings G. Impact of alcohol advertising and media exposure on adolescent alcohol use: a systematic review of longitudinal studies. *Alcohol Alcohol* 2009; **44:** 229–43.

356 Smith LA, Foxcroft DR. The effect of alcohol advertising, marketing and portrayal on drinking behaviour in young people: systematic review of prospective cohort studies. *BMC Public Health* 2009; **9:** 51.

357 Jernigan D, Noel J, Landon J, Thornton N, Lobstein T. Alcohol marketing and youth alcohol consumption: a systematic review of longitudinal studies published since 2008. *Addiction* 2017; **112** (suppl 1)**:** 7–20.

358 Lobstein T, Landon J, Thornton N, Jernigan D. The commercial use of digital media to market alcohol products: a narrative review. *Addiction* 2017; **112** (suppl 1)**:** 21–27.

359 EU. Directive (EU) 2018/1808 of the European Parliament and of the Council of 14 November 2018. Nov 28, 2018. https://eur-lex.europa.eu/eli/dir/2018/1808/oj (accessed Nov 4, 2021).

360 Burton R, Henn C, Lavoie D, et al. A rapid evidence review of the effectiveness and cost-effectiveness of alcohol control policies: an English perspective. *Lancet* 2017; **389:** 1558–80.

361 Cranwell J, Whittamore K, Britton J, Leonardi-Bee J. Alcohol and tobacco content in UK video games and their association with alcohol and tobacco use among young people. *Cyberpsychol Behav Soc Netw* 2016; **19:** 426–34.

362 VBF. Prohibition of alcohol advertising in Norway. September, 2018. https://www.nhomd.no/contentassets/2903e65252854beda11b61c0e8d41a2d/prohibition-of-alcohol-advertising-in-norway--0918.pdf (accessed Nov 4, 2021).

363 van Dalen W. Alcohol marketing restrictions in Europe. June, 2018. https://www.paho.org/en/file/50395/download?token=U_lazK-P (accessed Nov 4, 2021).

364 Gallopel-Morvan K, Spilka S, Mutatayi C, Rigaud A, Lecas F, Beck F. France's Évin Law on the control of alcohol advertising: content, effectiveness and limitations. *Addiction* 2017; **112** (suppl 1)**:** 86–93.

365 WHO. Monitoring and restricting digital marketing of unhealthy products to children and adolescents. 2019. https://www.euro.who.int/en/health-topics/disease-prevention/nutrition/publications/2019/monitoring-and-restricting-digital-marketing-of-unhealthy-products-to-children-and-adolescents-2019 (accessed Nov 4, 2021).

366 Baumberg B. World trade law and a framework convention on alcohol control. *J Epidemiol Community Health* 2010; **64:** 473–74.

367 Just Drinks. How to market alcohol where alcohol marketing is banned. March 16, 2016. https://www.just-drinks.com/features/how-to-market-alcohol-where-alcohol-marketing-is-banned-focus/ (accessed Nov 4, 2021).

368 Mialon M, Corvalan C, Cediel G, Scagliusi FB, Reyes M. Food industry political practices in Chile: "the economy has always been the main concern". *Global Health* 2020; **16:** 107.

369 Quintiliano Scarpelli D, Pinheiro Fernandes AC, Rodriguez Osiac L, Pizarro Quevedo T. Changes in nutrient declaration after the food labeling and advertising law in Chile: a longitudinal approach. *Nutrients* 2020; **12:** E2371.

370 Loos RJF, Yeo GSH. The genetics of obesity: from discovery to biology. *Nat Rev Genet* 2021; published online Sept 23. https://doi.org/10.1038/s41576-021-00414-z.

371 Visscher BB, Steunenberg B, Heijmans M, et al. Evidence on the effectiveness of health literacy interventions in the EU: a systematic review. *BMC Public Health* 2018; **18:** 1414.

372 Schwarzfuchs D, Golan R, Shai I. Four-year follow-up after two-year dietary interventions. *N Engl J Med* 2012; **367:** 1373–74.

373 Bray GA, Kim KK, Wilding JPH, World Obesity Federation. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. *Obes Rev* 2017; **18:** 715–23.

374 Skouteris H, Hill B, McCabe M, Swinburn B, Busija L. A parent-based intervention to promote healthy eating and active behaviours in pre-school children: evaluation of the MEND 2-4 randomized controlled trial. *Pediatr Obes* 2016; **11:** 4–10.

375 Yuksel HS, Şahin FN, Maksimovic N, Drid P, Bianco A. School-based intervention programs for preventing obesity and promoting physical activity and fitness: a systematic review. *Int J Environ Res Public Health* 2020; **17:** E347.

376 Martin A, Saunders DH, Shenkin SD, Sproule J. Lifestyle intervention for improving school achievement in overweight or obese children and adolescents. *Cochrane Database Syst Rev* 2014; **3:** CD009728.

377 Zelber-Sagi S, Bord S, Dror-Lavi G, et al. Role of illness perception and self-efficacy in lifestyle modification among non-alcoholic fatty liver disease patients. *World J Gastroenterol* 2017; **23:** 1881–90.

378 Haigh L, Bremner S, Houghton D, et al. Barriers and facilitators to mediterranean diet adoption by patients with nonalcoholic fatty liver disease in northern Europe. *Clin Gastroenterol Hepatol* 2019; **17:** 1364–71.

379 Zelber-Sagi S. Minding the gap between clinical trials and treatment with the Mediterranean dietary pattern for patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2019; **17:** 1248–50.

380 Nguyen VH, Yeo YH, Zou B, et al. Discrepancies between actual weight, weight perception and weight loss intention amongst persons with NAFLD. *J Intern Med* 2021; **289:** 840–50.

381 Larney S, Peacock A, Leung J, et al. Global, regional, and country-level coverage of interventions to prevent and manage HIV and hepatitis C among people who inject drugs: a systematic review. *Lancet Glob Health* 2017; **5:** e1208–20.

382 Lampertico P, Agarwal K, Berg T, et al. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; **67:** 370–98.

383 WHO. Prevention of mother-to-child transmission of hepatitis B virus: guidelines on antiviral prophylaxis in pregnancy. July 27, 2020. https://www.who.int/publications/i/item/978-92-4-000270-8 (accessed Nov 4, 2021).

384 Chaillon A, Rand EB, Reau N, Martin NK. Cost-effectiveness of universal hepatitis C virus screening of pregnant women in the United States. *Clin Infect Dis* 2019; **69:** 1888–95.

385 Thijssen M, Lemey P, Amini-Bavil-Olyaee S, et al. Mass migration to Europe: an opportunity for elimination of hepatitis B virus? *Lancet Gastroenterol Hepatol* 2019; **4:** 315–23.

386 WHO. Report on the health of refugees and migrants in the WHO European Region: no public health without refugee and migrant health. 2018. https://www.euro.who.int/en/publications/abstracts/report-on-the-health-of-refugees-and-migrants-in-the-who-european-region-no-public-health-without-refugee-and-migrant-health-2018 (accessed Nov 4, 2021).

387 Noori T, Hargreaves S, Greenaway C, et al. Strengthening screening for infectious diseases and vaccination among migrants in Europe: what is needed to close the implementation gaps? *Travel Med Infect Dis* 2021; **39:** 101715.

388 Walker JG, Kuchuloria T, Sergeenko D, et al. Interim effect evaluation of the hepatitis C elimination programme in Georgia: a modelling study. *Lancet Glob Health* 2020; **8:** e244–53.

389 Mokaya J, Burn EAO, Tamandjou CR, et al. Modelling cost-effectiveness of tenofovir for prevention of mother to child transmission of hepatitis B virus (HBV) infection in South Africa. *BMC Public Health* 2019; **19:** 829.

390 Chaillon A, Rand EB, Reau N, Martin NK. Cost-effectiveness of universal hepatitis C virus screening of pregnant women in the United States. *Clin Infect Dis* 2019; **69:** 1888–95.

391 Thokala P, Simpson EL, Tappenden P, et al. Ledipasvir-sofosbuvir for treating chronic hepatitis C: a NICE single technology appraisal—an evidence review group perspective. *PharmacoEconomics* 2016; **34:** 741–50.

392 Howell J, Pedrana A, Schroeder SE, et al. A global investment framework for the elimination of hepatitis B. *J Hepatol* 2021; **74:** 535–49.

393 Boccalini S, Taddei C, Ceccherini V, et al. Economic analysis of the first 20 years of universal hepatitis B vaccination program in Italy: an a posteriori evaluation and forecast of future benefits. *Hum Vaccin Immunother* 2013; **9:** 1119–28.

394 Iyengar S, Tay-Teo K, Vogler S, et al. Prices, costs, and affordability of new medicines for hepatitis C in 30 countries: an economic analysis. *PLoS Med* 2016; **13:** e1002032.

395 Heffernan A, Cooke GS, Nayagam S, Thursz M, Hallett TB. Scaling up prevention and treatment towards the elimination of hepatitis C: a global mathematical model. *Lancet* 2019; **393:** 1319–29.

396 Nayagam S, Sicuri E, Lemoine M, et al. Economic evaluations of HBV testing and treatment strategies and applicability to low and middle-income countries. *BMC Infect Dis* 2017; **17** (suppl 1)**:** 692.

397 The Global Fund. Pooled procurement mechanism reference pricing: ARVs. March 22, 2021. https://www.theglobalfund.org/media/10754/covid19_ppmreferencepricing_list_en.pdf (accessed Nov 1, 2021).

398 Ward Z, Reynolds R, Campbell L, et al. Cost-effectiveness of the HepCATT intervention in specialist drug clinics to improve case-finding and engagement with HCV treatment for people who inject drugs in England. *Addiction* 2020; **115:** 1509–21.

399 Jin H, Marshall BDL, Degenhardt L, et al. Global opioid agonist treatment: a review of clinical practices by country. *Addiction* 2020; **115:** 2243–54.

400 Platt L, Minozzi S, Reed J, et al. Needle and syringe programmes and opioid substitution therapy for preventing HCV transmission among people who inject drugs: findings from a Cochrane Review and meta-analysis. *Addiction* 2018; **113:** 545–63.

401 Grebely J, Tran L, Degenhardt L, et al. Association between opioid agonist therapy and testing, treatment uptake, and treatment outcomes for hepatitis C infection among people who inject drugs: a systematic review and meta-analysis. *Clin Infect Dis* 2020.

402 Lazarus JV, Safreed-Harmon K, Thursz MR, et al. The micro-elimination approach to eliminating hepatitis C: strategic and operational considerations. *Semin Liver Dis* 2018; **38:** 181–92.

403 Lazarus JV, Wiktor S, Colombo M, Thursz M. Micro-elimination—a path to global elimination of hepatitis C. *J Hepatol* 2017; **67:** 665–66.

404 Smit C, Boyd A, Rijnders BJA, et al. HCV micro-elimination in individuals with HIV in the Netherlands 4 years after universal access to direct-acting antivirals: a retrospective cohort study. *Lancet HIV* 2021; **8:** e96–105.

405 Boerekamps A, van den Berk GE, Lauw FN, et al. Declining hepatitis C virus (HCV) incidence in Dutch human immunodeficiency virus-positive men who have sex with men after unrestricted access to HCV therapy. *Clin Infect Dis* 2018; **66:** 1360–65.

406 Bartlett SR, Fox P, Cabatingan H, et al. Demonstration of near-elimination of hepatitis C virus among a prison population: the Lotus Glen Correctional Centre Hepatitis C Treatment Project. *Clin Infect Dis* 2018; **67:** 460–63.

407 McMahon BJ, Bulkow LR, Singleton RJ, et al. Elimination of hepatocellular carcinoma and acute hepatitis B in children 25 years after a hepatitis B newborn and catch-up immunization program. *Hepatology* 2011; **54:** 801–07.

408 Heffernan A, Cooke GS, Nayagam S, Thursz M, Hallett TB. Scaling up prevention and treatment towards the elimination of hepatitis C: a global mathematical model. *Lancet* 2019; **393:** 1319–29.

409 Lal A, Erondu NA, Heymann DL, Gitahi G, Yates R. Fragmented health systems in COVID-19: rectifying the misalignment between global health security and universal health coverage. *Lancet* 2021; **397:** 61–67.

410 Sipido KR, Antoñanzas F, Celis J, et al. Overcoming fragmentation of health research in Europe: lessons from COVID-19. *Lancet* 2020; **395:** 1970–71.

411 European Parliament. European Health Emergency Preparedness and Response Authority (HERA). Sept 20, 2021. https://www.europarl.europa.eu/legislative-train/theme-promoting-oureuropean-way-of-life/file-european-biomedical-research-anddevelopment-agency (accessed Nov 4, 2021).

412 European Commission. European Health Emergency preparedness and Response Authority (HERA): getting ready for future health emergencies. Sept 16, 2021. https://ec.europa.eu/commission/presscorner/detail/en/IP_21_4672 (accessed Nov 4, 2021).

413 Krugman P. Vaccines: a very European disaster. March 18, 2021. https://www.nytimes.com/2021/03/18/opinion/coronavirus-vaccine-europe.html (accessed Nov 4, 2021).

414 Sheron N, Gilmore I. Effect of policy, economics, and the changing alcohol marketplace on alcohol related deaths in England and Wales. *BMJ* 2016; **353:** i1860.

415 Stockwell T, Zhao J, Giesbrecht N, Macdonald S, Thomas G, Wettlaufer A. The raising of minimum alcohol prices in Saskatchewan, Canada: impacts on consumption and implications for public health. *Am J Public Health* 2012; **102:** e103–10.

416 Stockwell T, Zhao J, Martin G, et al. Minimum alcohol prices and outlet densities in British Columbia, Canada: estimated impacts on alcohol-attributable hospital admissions. *Am J Public Health* 2013; **103:** 2014–20.

417 Boniface S, Scannell JW, Marlow S. Evidence for the effectiveness of minimum pricing of alcohol: a systematic review and assessment using the Bradford Hill criteria for causality. *BMJ Open* 2017; **7:** e013497.

418 Angus C, Holmes J, Meier PS. Comparing alcohol taxation throughout the European Union. *Addiction* 2019; **114:** 1489–94.

419 Holmes J, Meng Y, Meier PS, et al. Effects of minimum unit pricing for alcohol on different income and socioeconomic groups: a modelling study. *Lancet* 2014; **383:** 1655–64.

420 Sharma A, Etilé F, Sinha K. The effect of introducing a minimum price on the distribution of alcohol purchase: a counterfactual analysis. *Health Econ* 2016; **25:** 1182–200.

421 Scotch Whisky Association and others (appellants) v The Lord Advocate and another (respondents). UKSC 76. UK Supreme Court; Scotland; Nov 15, 2017.

422 Goiana-da-Silva F, Cruz-E-Silva D, Allen L, et al. Modelling impacts of food industry co-regulation on noncommunicable disease mortality, Portugal. *Bull World Health Organ* 2019; **97:** 450–59.

423 WHO. Guiding principles and framework manual for front-of-pack labelling for promoting healthy diet. May 13, 2019. https://apps.who.int/nutrition/publications/policies/guidingprinciples-labelling-promoting-healthydiet/en/index.html (accessed Nov 4, 2021).

424 Crockett RA, King SE, Marteau TM, et al. Nutritional labelling for healthier food or non-alcoholic drink purchasing and consumption. *Cochrane Database Syst Rev* 2018; **2:** CD009315.

425 WHO. From burden to "best buys": reducing the economic impact of non-communicable diseases in low- and middle-income countries. 2011. https://www.who.int/nmh/publications/best_buys_summary.pdf (accessed Nov 4, 2021).

426 Schwarz JM, Noworolski SM, Erkin-Cakmak A, et al. Effects of dietary fructose restriction on liver fat, de novo lipogenesis, and insulin kinetics in children with obesity. *Gastroenterology* 2017; **153:** 743–52.

427 Schwimmer JB, Ugalde-Nicalo P, Welsh JA, et al. Effect of a low free sugar diet vs usual diet on nonalcoholic fatty liver disease in adolescent boys: a randomized clinical trial. *JAMA* 2019; **321:** 256–65.

428 WHO. Fiscal policies for diet and the prevention of noncommunicable diseases: technical meeting report, 5–6 May 2015, Geneva, Switzerland. 2016. http://apps.who.int/iris/handle/10665/250131 (accessed Nov 4, 2021).

429 Cancer Research UK. Sugar tax could prevent 3.7 million cases of obesity over next decade. Feb 19, 2016. https://news.cancerresearchuk.org/2016/02/19/sugar-tax-could-prevent-37-million-cases-of-obesity-over-next-decade/ (accessed Nov 4, 2021).

430 Willett W, Rockström J, Loken B, et al. Food in the Anthropocene: the EAT–*Lancet* Commission on healthy diets from sustainable food systems. *Lancet* 2019; **393:** 447–92.

431 Mullish BH, Kabir MS, Thursz MR, Dhar A. Review article: depression and the use of antidepressants in patients with chronic liver disease or liver transplantation. *Aliment Pharmacol Ther* 2014; **40:** 880–92.

432 Durazzo M, Belci P, Collo A, et al. Gender specific medicine in liver diseases: a point of view. *World J Gastroenterol* 2014; **20:** 2127–35.

433 European Association for the Study of the Liver (EASL). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016; **64:** 1388–402.

434 EU. The 2021 Ageing Report: underlying assumptions and projection methodologies. Nov 20, 2020. https://ec.europa.eu/info/publications/2021-ageing-report-underlying-assumptions-and-projection-methodologies_en (accessed Nov 4, 2021).

435 Colombo M. EASL Clinical Practice Guidelines for the management of occupational liver diseases. *Liver Int* 2020; **40** (suppl 1): 136–41.