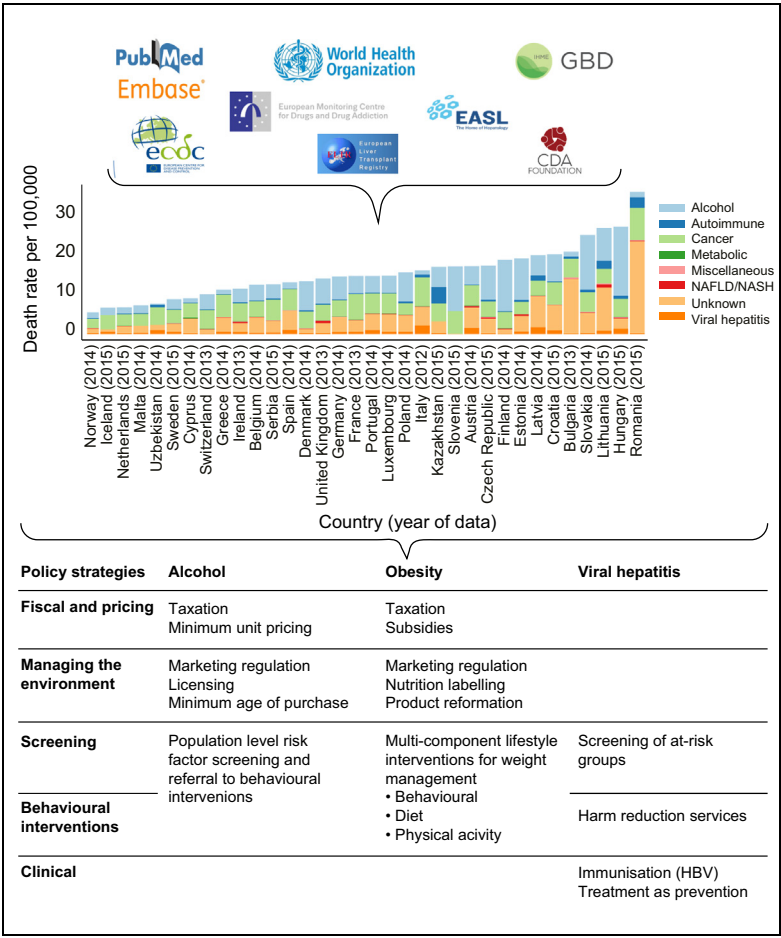


# Burden of liver disease in Europe: Epidemiology and analysis of risk factors to identify prevention policies

Graphical abstract



Authors

Laura Pimpin, Helena Cortez-Pinto, Francesco Negro, ..., Jeffrey V. Lazarus, Laura Webber, Nick Sheron

Correspondence

nick.sheron@soton.ac.uk  
(N. Sheron)

Summary

The burden of liver disease in Europe continues to grow. We aimed to describe the epidemiology of liver diseases and their risk factors in European countries, identifying public health interventions that could impact on these risk factors to reduce the burden of liver disease. As part of the HEPAHEALTH project we extracted information on historical and current prevalence and mortality from national and international literature and databases on liver disease in 35 countries in the World Health Organization European region, as well as historical and recent prevalence data on their main determinants; alcohol consumption, obesity and hepatitis B and C virus infections. We extracted information from peer-reviewed and grey literature to identify public health interventions targeting these risk factors. The epidemiology of liver disease is diverse, with variations in the exact composition of diseases and the trends in risk factors which drive them. Prevalence and mortality data indicate that increasing cirrhosis and liver cancer may be linked to dramatic increases in harmful alcohol consumption in Northern European countries, and viral hepatitis epidemics in Eastern and Southern European countries. Countries with historically low levels of liver disease may experience an increase in non-alcoholic fatty liver disease in the future, given the rise of obesity across most European countries. Liver disease in Europe is a serious issue, with increasing cirrhosis and liver cancer. The public health and hepatology communities are uniquely placed to implement measures aimed at reducing their causes: harmful alcohol consumption, child and adult obesity, and chronic infection with hepatitis viruses, which will in turn reduce the burden of liver disease.



# Burden of liver disease in Europe: Epidemiology and analysis of risk factors to identify prevention policies

Laura Pimpin<sup>1</sup>, Helena Cortez-Pinto<sup>2</sup>, Francesco Negro<sup>3</sup>, Emily Corbould<sup>1</sup>, Jeffrey V. Lazarus<sup>4,5</sup>, Laura Webber<sup>1</sup>, Nick Sheron<sup>6,\*</sup>, and the members of the EASL HEPAAHEALTH Steering Committee<sup>†</sup>

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## Summary

The burden of liver disease in Europe continues to grow. We aimed to describe the epidemiology of liver diseases and their risk factors in European countries, identifying public health interventions that could impact on these risk factors to reduce the burden of liver disease. As part of the HEPAAHEALTH project we extracted information on historical and current prevalence and mortality from national and international literature and databases on liver disease in 35 countries in the World Health Organization European region, as well as historical and recent prevalence data on their main determinants; alcohol consumption, obesity and hepatitis B and C virus infections. We extracted information from peer-reviewed and grey literature to identify public health interventions targeting these risk factors. The epidemiology of liver disease is diverse, with variations in the exact composition of diseases and the trends in risk factors which drive them. Prevalence and mortality data indicate that increasing cirrhosis and liver cancer may be linked to dramatic increases in harmful alcohol consumption in Northern European countries, and viral hepatitis epidemics in Eastern and Southern European countries. Countries with historically low levels of liver disease may experience an increase in non-alcoholic fatty liver disease in the future, given the rise of obesity across most European countries. Liver disease in Europe is a serious issue, with increasing cirrhosis and liver cancer. The public health and hepatology communities are uniquely placed to implement measures aimed at reducing their causes: harmful alcohol consumption, child and adult obesity, and chronic infection with hepatitis viruses, which will in turn reduce the burden of liver disease.

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## Introduction

Europe has the largest burden of liver disease in the world,<sup>1</sup> with the burden expected to grow across many countries. However, the current and historical epidemiology of liver disease varies between countries within Europe. For example, Finland and the UK have observed staggering increases in liver disease mortality over the last 40 years while the inverse is true for countries such as France and Italy, where liver disease mortality began declining in the 1970s and has kept falling, largely because of effective policy and population-level measures.

Differences in liver disease epidemiology occur in part because of the prevalence of modifiable risk factors, such as harmful alcohol consumption, obesity, and viral hepatitis. Worryingly, Europe has the highest per capita alcohol consumption and alcohol-related loss of disability adjusted life years of any of the global WHO regions.<sup>2</sup> Obesity has increased markedly over the past four decades,<sup>3,4</sup> and as a result, non-alcoholic fatty liver disease (NAFLD) is an increasingly prevalent liver disease in Europe.<sup>2</sup> The prevalence of viral hepatitis is less well documented.<sup>2</sup> Prevention of these risk factors and types of liver disease is important in order to stop progression to other forms of liver disease, such as liver cancer. Liver disease principally affects working age people. Therefore, tackling risk factors will not only impact the

individual and health system, but also the economy and business sectors.

Differences in demographics, geography, and historical factors need to be considered when trying to understand the variance in liver disease risk factors, morbidity and mortality, as well as the interventions that best reduce the burden of liver disease. Importantly, liver disease risk factors are amenable to prevention and treatment, so liver disease can be reduced and deaths can be averted. Understanding the magnitude of liver disease prevalence, how and why it has changed over time, and what works to reduce the population's risk is imperative if countries are to learn from each other and act to reduce the burden.

## Aim

The European Association for the Study of the Liver (EASL) HEPAAHEALTH project, summarised in a report, was commissioned to: i) collect and analyse data in order to best describe the burden of liver disease across 35 European countries (including all 28 European Union [EU] countries); ii) collect data on the largest, modifiable determinants of liver disease (alcohol, obesity and viral hepatitis) and describe their changes over time; and iii) review the evidence on policies or interventions that could reduce the exposure to these risk factors at a population level.

<sup>1</sup>UK Health Forum, London, United Kingdom;

<sup>2</sup>Departamento de Gastroenterologia, CHLN, Laboratório de Nutrição, Faculdade de Medicina, Universidade de Lisboa, Portugal;

<sup>3</sup>Divisions of Gastroenterology and Hepatology and Clinical Pathology, University Hospitals of Geneva, Geneva, Switzerland;

<sup>4</sup>Barcelona Institute for Global Health (ISGlobal), Hospital Clinic, University of Barcelona, Barcelona, Spain;

<sup>5</sup>CHIP, Rigshospitalet, University of Copenhagen, Øster Alle 56, 5. sal, DK-2100 Copenhagen, Denmark;

<sup>6</sup>University of Southampton, Southampton SO17 1BJ, United Kingdom

\* Corresponding author.  
Address: CES Academic Unit  
University of Southampton Level  
E, MP(811), South  
Academic Block, University  
Hospital Southampton,  
Tremona Road, Southampton  
SO16 6YD, United Kingdom.  
Tel.: +44 02381 205232.  
E-mail address: [nick.sheron@soton.ac.uk](mailto:nick.sheron@soton.ac.uk) (N. Sheron).

## Methods

In order to maximise comparability across countries, and to use a standardised definition of liver disease, the majority of data on the epidemiology of liver disease and its risk factors were obtained for 35 countries (see Table 1 from online databases). It was beyond the scope of this study to include all 53 World Health Organization (WHO) European Region countries. The EU-28 countries were chosen plus additional countries where the study team had particular expertise and interest Table 2.

## Data collection

When insufficient data were available, additional sources of information were collected from a comprehensive review of the peer-reviewed and grey literature (that is, resources produced outside of the traditional academic publishing, such as reports from non-academic organisations) and identifying experts through the referral of other experts ("snowballing" of contacts) in the field of liver disease.

The WHO European Detailed Mortality Data<sup>5</sup> database combined raw mortality rates for 1994 to 2015 into eight broad liver disease categories (including alcoholic liver disease, NAFLD and viral hepatitis). This data was supplemented with data from WHO European Health for All database for broader categories of liver disease (1970 to 2015).<sup>6</sup>

The Global Burden of Disease (GBD) study (2016)<sup>1</sup> provided prevalence estimates of cirrhosis, other chronic liver diseases and liver cancer caused by alcohol, hepatitis B, hepatitis C or other causes for the years 1990 to 2016.

Data on liver transplantation in Europe was obtained from the European Liver Transplantation Registry (ELTR).<sup>7</sup>

Chronic hepatitis B and C prevalence data were obtained from the European Centres for Disease Prevention and Control (ECDC)<sup>8</sup> and were complemented by hepatitis B and C modelled prevalence estimates from the Polaris Observatory.<sup>9,10</sup> In addition, published reviews of the latest data were used to triangulate infection prevalence, and data on prevalence of hepatitis B and C in people who inject drugs (PWID) were obtained from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA).<sup>11</sup>

Average annual current consumption in litres of pure alcohol for total alcohol, beer, wine and spirits was extracted from the WHO European Health for All databases, for 1970 to 2015. Obesity prevalence data from 1993 to 2015 was obtained from a previous report commissioned by the WHO.<sup>3,12</sup> This project collected historical national prevalence data from a variety of national or regional sources. The sources for this can be found in the HEPAAHEALTH report.

Country-level type 2 diabetes prevalence data for 2007 to 2015 in adults was obtained from the

International Diabetes Federation Diabetes Atlas project.<sup>13</sup> Information on injecting drug use, as one of the modes of transmission for hepatitis B and C was also collected from the EMCDDA.<sup>11</sup>

## Analysis

Data on the prevalence and mortality of liver disease, and on the distribution of the largest modifiable risk factors for liver disease were analysed to present time trends, differences across sub-regions (UN Eastern, Northern, Southern and Western regions) and individual countries within these sub-regions. The historical trends in mortality and prevalence were overlaid with plots of alcohol consumption and obesity prevalence.

A comprehensive review of PubMed, Embase, and Google Scholar was conducted to identify peer-reviewed and grey literature reviews that provided evidence on public health interventions aimed at reducing or preventing risk factors of liver disease, in particular, alcohol consumption, obesity and diabetes and chronic viral hepatitis. No language restrictions were applied.

## General data

### Present situation

Data on prevalence of liver disease was collected using the GBD 2016 project data.<sup>1</sup> The categories of liver disease present in the dataset are cirrhosis and chronic liver disease, the other being liver cancer. Cirrhosis and chronic liver disease are further broken down into four aetiologic categories: alcohol use, hepatitis B infection, hepatitis C infection and other causes. The age-adjusted prevalence for the latest year in the 35 countries for males and females, ranged from 447 (Iceland) to 1,100 (Romania) cases per 100,000, with a median of 833 (Fig. 1) relative contribution of these aetiologies follows a geographical pattern, with alcohol being predominant in Western countries and viral hepatitis B and C more prevalent in Eastern countries. In Central European countries, alcohol and viral hepatitis contribute equally to the burden of disease, with the caveat that GBD data is modelled. Hepatitis C is the most prevalent cause of viral hepatitis in most countries, with the exception of Kazakhstan and Uzbekistan, where hepatitis B is more frequent.

Interestingly, when it concerns liver cancer, a north-south gradient is found, as illustrated in

<sup>†</sup>Collaborators: Members of the EASL HEPAAHEALTH Steering Committee  
Patrizia Burra<sup>a</sup>, Olav Dalgard<sup>b</sup>, Goran Jankovic<sup>c</sup>, Jerzy Jaroszewicz<sup>d</sup>, Jeffrey V. Lazarus<sup>e</sup>, Ansgar W. Lohse<sup>f</sup>, Valery Lunkov<sup>g</sup>, Marina Mayevskaya<sup>h</sup>, Alexander Nersesov<sup>i</sup>, Marieta Simonova<sup>j</sup>

<sup>a</sup>Gastroenterology, Department of Surgery, Oncology and Gastroenterology, Padova University Hospital, Padua, Italy;

<sup>b</sup>Akershus University Hospital, Lørenskog, Norway;

<sup>c</sup>Clinic for Gastroenterology and Hepatology, Clinical Centre of Serbia, School of Medicine, University of Belgrade, Serbia;

<sup>d</sup>Department of Infectious Diseases and Hepatology, Medical University of Silesia, Katowice, Poland;

<sup>e</sup>Barcelona Institute for Global Health (ISGlobal), Hospital Clínic, University of Barcelona, Barcelona, Spain;

<sup>f</sup>Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;

<sup>g</sup>Department of Hepatology, Vasilenko Clinic of Internal Diseases, Department of Internal Medicine, Russia;

<sup>h</sup>Department of Internal Medicine, I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Moscow, Russia;

<sup>i</sup>National Research Institute of Cardiology and Internal Diseases, Almaty, Kazakhstan;

<sup>j</sup>Department of Gastroenterology, HPB Surgery and Trans-

### Key point

In modelled data from GBD, alcohol is the predominant aetiology of liver disease in most countries with a high prevalence of viral hepatitis B and C in Central and Eastern Europe.

**Table 1. List of countries included in the HEPAAHEALTH project.**

Austria	Belgium	Bulgaria	Croatia	Cyprus
Czech Republic	Denmark	Estonia	Finland	France
Germany	Greece	Hungary	Iceland	Ireland
Italy	Kazakhstan	Latvia	Lithuania	Luxembourg
Malta	Netherlands	Norway	Poland	Portugal
Romania	Russia	Serbia	Slovakia	Slovenia
Spain	Sweden	Switzerland	United Kingdom	Uzbekistan

**Table 2. Summary of main findings of meta-review of systematic reviews on fiscal policies on diet (reproduced with permission).**

	Food/beverage taxes	Nutrient-focused taxes	Subsidies
Effect on consumption	Strongest evidence for SSB taxes – reduce consumption by same percentage as tax rate.	Reduce consumption of target but may increase consumption of non-target nutrients; may apply to core foods; better if paired with subsidy.	Subsidies increase healthy food intake. Strongest evidence for fruit and vegetable subsidies.
Effects on body weight/disease outcomes	Substitution will affect total calorie intake. Most effective to target SSBs. Limited evidence for disease outcomes.	Disease outcome affected by substitution – nutrient profile taxes less likely to have unintended effects than single nutrient-based taxes.	Subsidies may also increase total calorie intake and body weight. Very likely to reduce dietary NCD risk factors.
Differential effects	May be most effective for low-income populations; may have greater effect on those who consume most.	May be more likely to have regressive effects as more likely to apply to core foods.	Mixed socioeconomic status effects for population subsidies, may benefit wealth. Targeted low-income subsidies effective.

Source: World Health Organization (2016). Fiscal policies for diet and prevention of noncommunicable diseases: technical meeting report, 5–6 May 2015, Geneva, Switzerland. World Health Organization. <http://www.who.int/iris/handle/10665/250131>.

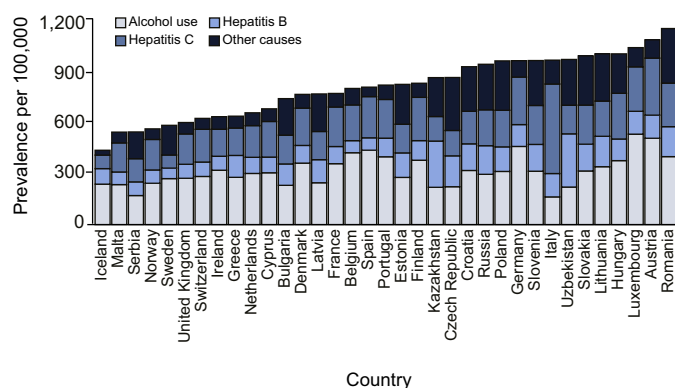
the wider HEPAHEALTH report, ranging from less than 2 cases per 100,000 to 15 cases per 100,000. Regarding the year 2015, the predominant aetiology of the underlying liver disease was viral hepatitis in the majority of countries, followed by alcohol use (see the wider HEPAHEALTH report).

Mortality data comes from ICD coding of death certification records collected by WHO, using the primary cause of death. As a result, there is likely to be an underestimation of the true liver disease associated mortality. Notwithstanding, there is a good correlation with the prevalence data, as seen in Fig. 2, again showing Romania with the highest (36 per 100,000), and Iceland and Norway with the lowest death rates (below 10 per 100,000). Mortality rates shown (Fig. 2) represent a total of 151,513 deaths from liver disease, in the last year of available data on deaths for all European countries combined, ranging from 33 deaths in Iceland in 2015 to 23,533 in Germany in 2014.

When looking at the consequent years of life lost, a very specific pattern is shown for liver diseases, with a higher rate of working life years lost vs. non-working life years lost, than most frequent chronic diseases such as ischaemic heart disease. This is mostly because two-thirds of liver disease patients die before 65 years of age.

### Key point

A worrying trend is the rising rate of liver cancer mortality in most European countries.



Source: Global Burden of Disease database

**Fig. 1. Age-standardised prevalence of cirrhosis and other liver diseases by aetiology in 2016 – modelled data.**<sup>1</sup> Median prevalence for alcohol use: 312 per 100,000; median prevalence for hepatitis B 130 per 100,000; median prevalence for hepatitis C: 212 per 100,000, median prevalence for other causes 116 per 100,000.

### Trends

The analysis of trends of cirrhosis and chronic liver disease in different countries may help understand the utility or disadvantages of different political and public health measures. Diverse patterns of evolution in mortality rate were observed in the timeframe of 1970–2015 for the 34 HEPAHEALTH countries (not including Russia), as shown (Fig. 3). Countries of Southern and Western Europe displayed a significant decrease in mortality rate (Austria, Croatia, France, Germany, Greece, Italy, Luxembourg, Portugal, Slovenia, Spain and Switzerland), while conversely, Eastern and Northern countries such as Bulgaria, Estonia, Finland, Hungary, Kazakhstan, Latvia, Lithuania, Romania and the UK, faced a significant increase. Yet, another group of countries remained stable-high (Slovakia and Uzbekistan), while others remained stable-low (Belgium, Cyprus, Czech Republic, Denmark, Iceland, Ireland, Malta, Netherlands, Norway, Poland, Serbia and Sweden).

A concerning trend in liver cancer mortality rates, is the recognisable increase in the large majority of countries (Austria, Czech Republic, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Portugal, Romania and the UK), although some countries have experienced small decreases in liver-related mortality (Bulgaria, Hungary, Kazakhstan, Poland and Spain). Again, other countries remained stable, either high or low (available in the HEPAHEALTH report).

In the next sections, more detailed information regarding epidemiological data, risk factors and political interventions will be described for each of the major liver disease aetiologies: alcohol-related, non-alcoholic fatty liver and viral hepatitis.

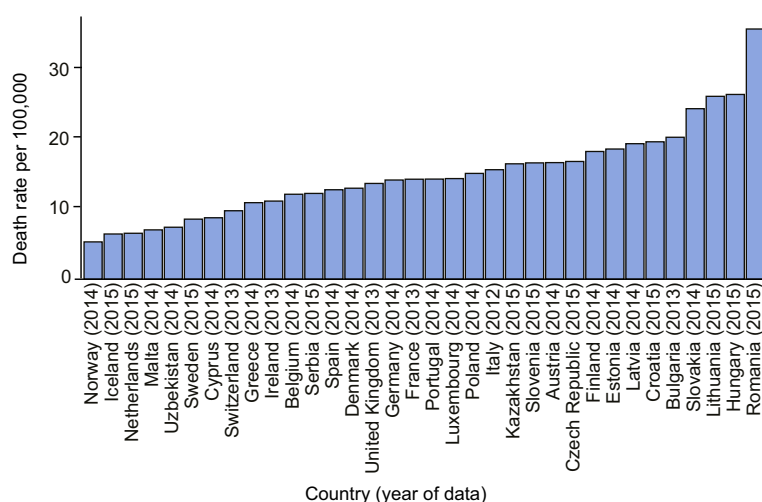
### Alcohol consumption and liver disease

According to the WHO, alcohol is a dose-related risk factor for more than 200 diseases. It causes 5.9% of all deaths globally and more than 25% of deaths in the age group 20–39 years.<sup>14</sup> For most diseases including cancer and hypertension, the dose relationship is linear starting at zero, i.e. there is no safe threshold for alcohol consumption.<sup>15</sup> Importantly, for liver disease the relation-



ship is exponential, with very heavy drinkers or extreme drinkers comprising a large proportion of patients with alcohol-related cirrhosis.<sup>15,16</sup> In addition to this, alcohol synergises with other risk factors for liver disease such as obesity and viral infections. For a body mass index (BMI) over 35 kg/m<sup>2</sup>, the hepatotoxicity of alcohol doubles: two bottles of wine per week effectively becomes four bottles as far as the liver is concerned.<sup>17</sup> Similarly, with hepatitis C virus (HCV) infection, alcohol consumption of more than 20 g per day (17.5 cl per week) increases mortality by 2.5-fold.<sup>18</sup> In a Danish series of 5,779 HCV infected individuals, 57% of patients with cirrhosis also had evidence of alcohol misuse.<sup>19</sup>

The European region has the highest levels of reported *per capita* alcohol consumption of any region.<sup>20</sup> Total alcohol consumption is summarised in the WHO European Health for All database (HFA-DB) as annual total litres of pure alcohol consumed *per capita* in individuals aged over 15 years. Four groups of countries emerged based on time trends for this consumption: Increasing trend, decreasing trend, stable-high trend and stable-low trend (Fig. 3). Although these trends are seen at national levels, alcohol consumption patterns are clustered within countries. For example the share of total alcohol consumed by the top 20% heaviest drinkers ranges from 50% in France and Switzerland, to above 80% in Hungary, based on national survey estimates by the Organisation for Economic Co-operation and Development (OECD).<sup>20</sup> Demographic patterns in alcohol consumption are changing too: consumption among younger people and women is growing while age of taking up drinking is decreasing.



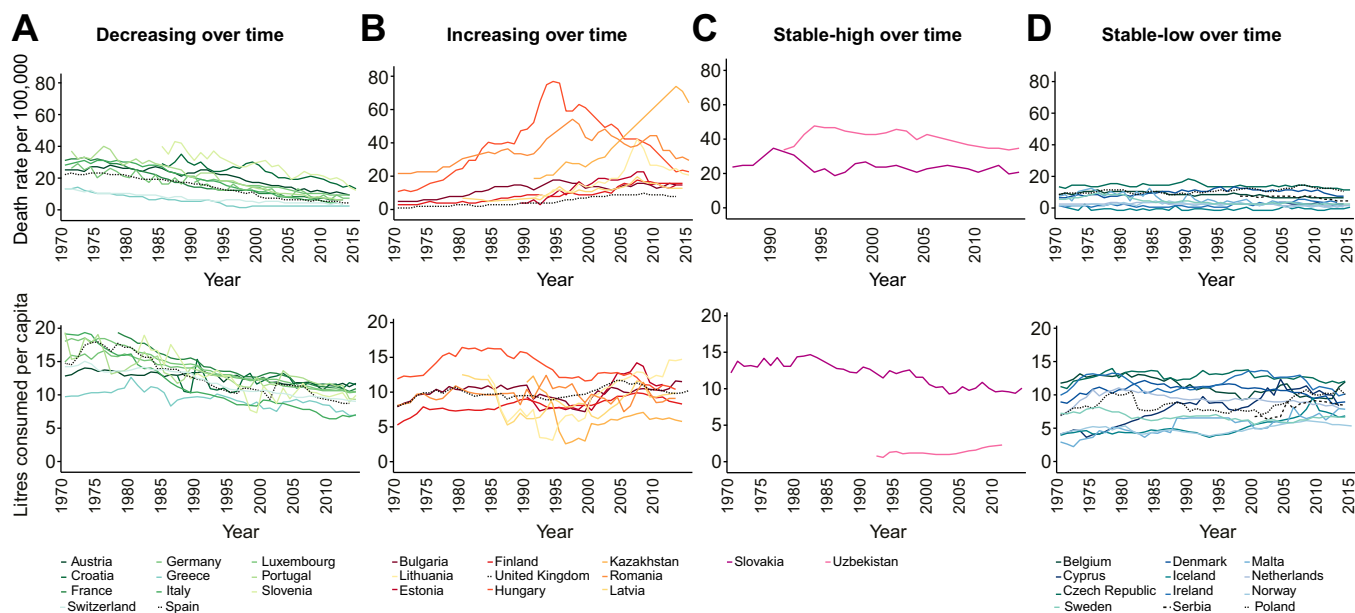
Source: WHO detailed mortality database (raw data)

Fig. 2. Age-standardised mortality for all liver diseases – in most recent year.<sup>5</sup>

Patterns of drinking, including frequency, average consumption and type of alcohol consumed, have differential effects on mortality and risk of disease.<sup>21</sup>

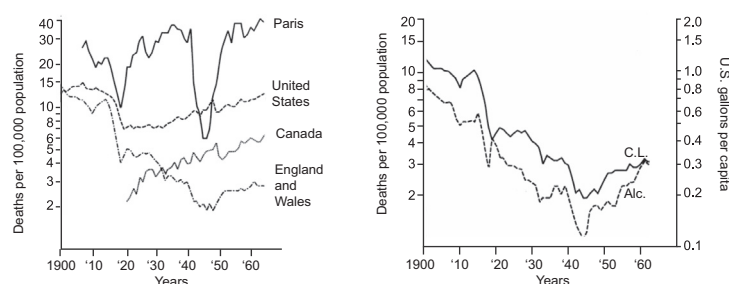
### The relationship between alcohol consumption and liver mortality

The strong relationship between population-level alcohol consumption and population-level liver mortality, was detailed in a seminal paper by Milton Terris in 1967,<sup>22</sup> who demonstrated that dramatic falls in cirrhosis mortality followed some world events, such as alcohol rationing in both world wars (Fig. 4).



Source: WHO Health for all database

Fig. 3. Total mortality from cirrhosis (top) and alcohol consumption (bottom) over time, for ages >15 years for countries in different trend groups. (A) Decreasing, (B) increasing, (C) stable-high, (D) stable-low.<sup>5</sup>



**Fig. 4. Death rates, cirrhosis of the liver and alcohol consumption reproduced with permission from Terris (1967).<sup>22</sup>**

### Key point

Evidence on the effectiveness on interventions to reduce alcohol consumption is strong and consistent in reviews by a number of major health bodies; taxation and price regulation are the most effective and cost-effective means to reduce alcohol related mortality.

An important aspect of this analysis that only recently received the attention it deserves<sup>23</sup> was that the link was between strong alcohol (wine and spirits) and cirrhosis mortality. For example, in the UK the consumption of weak beer in pubs could be excluded from the model (Fig. 4).<sup>23,24</sup> This makes sense, as by the time most patients with alcohol-related liver disease have graduated to cirrhosis, the majority are drinking strong alcohol.<sup>16</sup>

These two principles are critical to understanding the relationship between alcohol consumption and cirrhosis mortality today. Substantial falls in overall alcohol consumption in France were associated with equally substantial falls in cirrhosis mortality, with no real differential impact by beverage type (Fig. 5). Similar changes have occurred in Italy and Spain.

While fourfold increases in mortality from chronic liver disease in the UK have followed relatively modest increases in overall alcohol consumption, the key difference is that consumption has shifted from weak beer consumed in pubs, to stronger alcohol (wine, spirits and strong cider) bought cheaply and drunk at home.<sup>15,25</sup>

In Finland rapid and substantial increases in liver mortality occurred in the early 2000's when Estonia joined the EU and import controls were relaxed, leading to a flood of cheap alcohol, but with little change in overall recorded alcohol consumption (Fig. 6). The subsequent policy response, including an increase in alcohol tax rates and changes in the availability of alcohol, effectively curtailed the increase, and liver mortality stabilised albeit at a higher level than before.<sup>26–28</sup>

The ecological correlation between alcohol consumption trends and mortality from alcoholic liver disease and mortality from any chronic liver disease and cirrhosis also holds for countries with stable patterns of alcohol intake. For example, the Czech Republic has a relatively high alcohol consumption trend which is apparently unchanged over time (Fig. 5).

### Interventions to reduce alcohol consumption and harm from alcohol

The evidence on the effectiveness of alcohol policy is strong and consistent in reviews by the WHO,<sup>29</sup>

OECD,<sup>20</sup> Public Health England<sup>15</sup> and others.<sup>30,31</sup> Public health approaches include population-level policies such as fiscal policies, policies regulating the marketing of alcohol and policies managing the drink environment and availability of alcohol, as well as individual-level interventions like screening, brief interventions and alcohol treatment.<sup>25,32–37</sup>

### Fiscal policy

As with tobacco, the most effective and cost effective means to reduce alcohol-related harm is to decrease the affordability of alcohol through fiscal policy.<sup>38–40</sup> The OECD report on Tackling Harmful Alcohol Use highlights excise duties and value added taxes as the most common combined approach.<sup>20</sup> The effect of increased alcohol taxation on consumption depends on the degree to which the tax is passed on to consumers and the most recent development in alcohol policy is the concept of setting a minimum price for a unit of alcohol (MUP).<sup>20,32,36</sup> This model was implemented in the Canadian province of British Columbia and as a result there have been dramatic reductions in liver disease mortality, despite increasing densities of private liquor stores during the same period.<sup>41</sup>

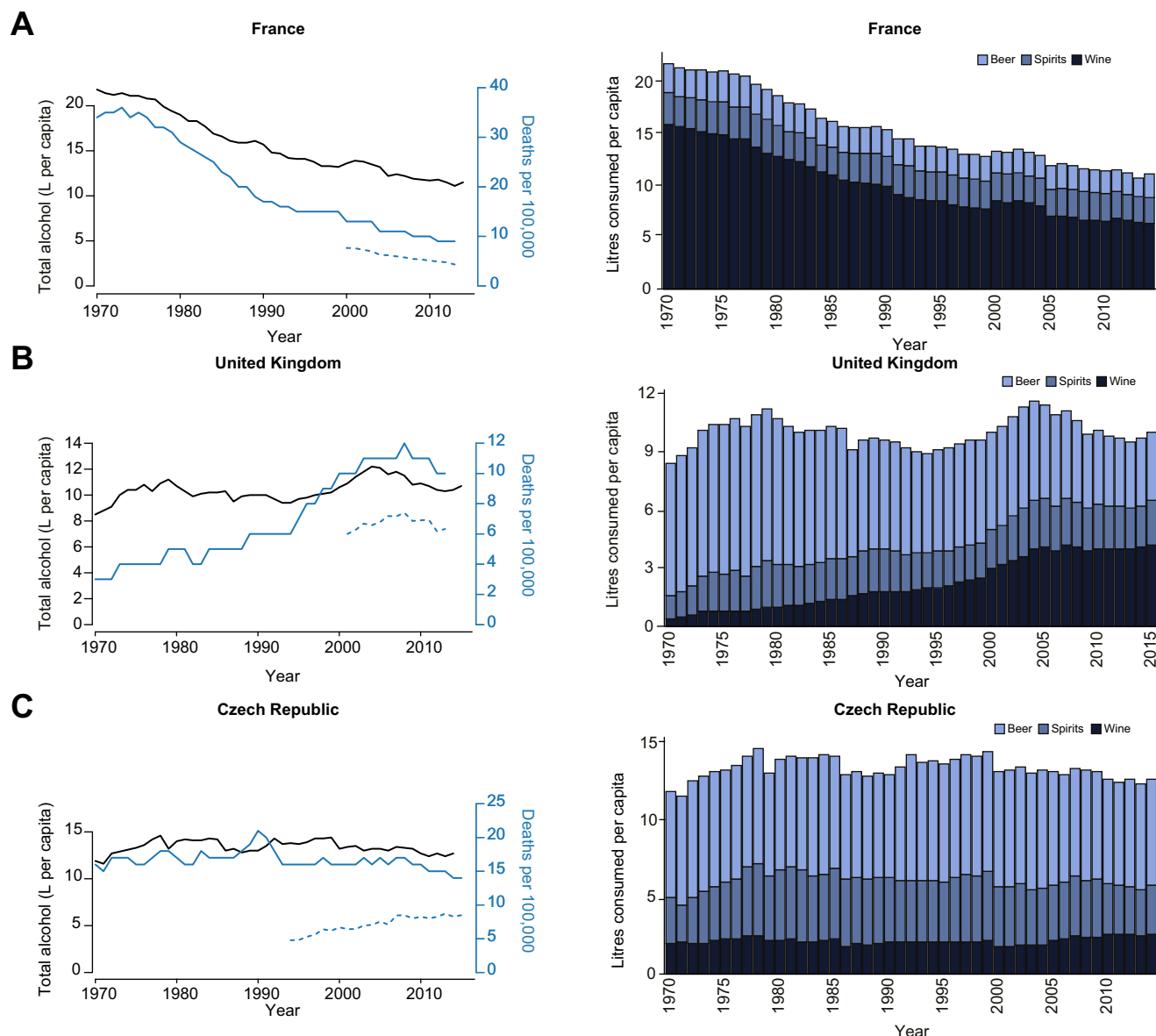
Legislation enabling the introduction of MUP was passed in Scotland in 2012, despite legal challenges by the Scotch Whiskey Association, as justification of strong public health grounds overruled the commercial considerations. MUP legislation was specifically targeted at the very cheap alcohol preferred by the extreme drinker who develop cirrhosis, and thus is more likely to be effective than tax or duty increases.<sup>42,43</sup>

In-depth summaries of studies estimating the effect of alcohol policy scenarios, modelling studies, natural experiments and case-studies, on alcohol consumption, hospital admissions and liver disease mortality are available in the wider HEPA-HEALTH report.

### Marketing restriction

After tobacco, the marketing of which has been regulated, alcohol is the most dangerous and unhealthy commodity currently marketed in Europe.<sup>44</sup> The landscape for alcohol marketing is changing and uses multiple avenues (radio, television sports events, celebrity endorsements, websites, product placement, social media, and others).<sup>44</sup> The marketing of alcoholic beverages is one of the 10 areas for policy action in the WHO Global strategy to reduce the harmful use of alcohol.

The evidence was reviewed recently by Babor and colleagues<sup>44</sup> who found positive associations between exposure to marketing and some measure of subsequent drinking behaviour and/or negative consequences of drinking.<sup>45</sup> For digital marketing there was a need 'for policies to control and restrict alcohol promotion, and especially to



Source: WHO Health for ALL database & WHO detailed mortality database (raw data)

**Fig. 5. Alcohol consumption and age-standardised mortality from cirrhosis and chronic liver diseases (blue filled) on the left and alcoholic liver disease mortality (blue dashed) (left) and total consumption of alcohol by type of alcohol ages >15 yr (right) in four countries. (A) France, (B) UK, (C) Czech Republic.<sup>6</sup>**

protect underage youth from commercial incentives to engage in drinking behaviour.<sup>46</sup> This suggests that current systems of self-regulation would need major modifications if they are to serve public health objectives.<sup>47,48</sup> They concluded that regulations should be statutory, enforced not by the alcohol industry, but by a public health agency and that global agreement on the marketing of alcoholic beverages would support national efforts to move towards a comprehensive ban on alcohol advertising, promotion and sponsorship.

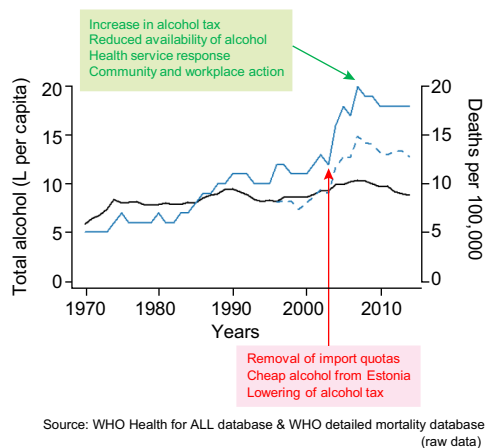
#### Screening and behavioural interventions

A recent narrative review of 24 systematic reviews was conducted on the effect of brief alcohol intervention effects. The authors reported that brief interventions were consistently reported to

be effective for addressing hazardous and harmful drinking in primary healthcare, and particularly in middle-aged, male drinkers.<sup>49</sup>

A recent review of 20 trials in public healthcare settings and eight in emergency departments confirmed that brief interventions to reduce alcohol consumption are associated with reducing weekly alcohol consumption among hazardous and harmful drinkers at 6 and 12 month follow-up.<sup>50</sup> In primary health care, brief interventions resulted in 31 g/week reduction in alcohol intake after 12 months, and 18 g/week for interventions in emergency departments.

The Lancet Liver Commission identified late diagnosis of liver disease as perhaps the most important clinical issue, and estimated that around 75% of patients with fatal cirrhosis were



**Fig. 6. Trends in liver mortality in Finland following entry of Estonia into the EU, a dramatic increase in liver mortality was stabilised by a strong policy response.**

unaware of their disease until presenting as an emergency with acute-on-chronic liver failure or variceal bleeding. A liver disease admission can have a profound impact on alcohol misuse, with around 40% of individuals becoming abstinent as a result<sup>51,52</sup> and some evidence that earlier primary care based liver diagnosis may also promote behaviour change.<sup>53</sup> As a result screening for liver disease in harmful and dependent drinkers has been recommended by the UK based National Institute for Health and Care Excellence,<sup>54</sup> further research will be needed to judge whether this approach can reduce liver mortality and morbidity.

### Obesity, diabetes and NAFLD The current and historical burden

The main risk factors that have been associated with NAFLD are obesity (predominantly central adiposity) as well as type 2 diabetes. The time trend in NAFLD/non-alcoholic steatohepatitis (NASH) mortality from WHO detailed data are presented (Fig. 7).<sup>5</sup> NAFLD/NASH represents only a very small proportion of liver-related-deaths in Europe, when analysing it as the primary cause

of death, although it is unlikely that these codes represent the current understanding on NAFLD or NASH.

In fact, the attributed codes do not enable recognition of NASH-related cirrhosis. Also, in the presence of other concomitant diagnosis such as alcohol or viral hepatitis these are recorded as the first cause of disease. Furthermore, the major cause of death in patients with NAFLD/NASH is cardiovascular.<sup>55</sup> NAFLD coded as the cause of death is only starting to appear in Ireland, Luxembourg, Hungary and the UK, countries where obesity is high (>23%).

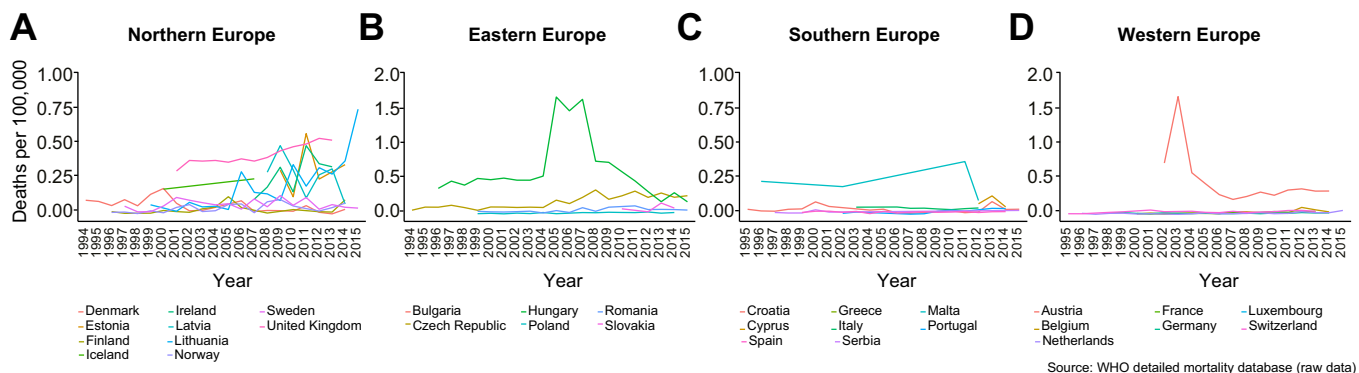
It is difficult to ascertain the true prevalence of NAFLD, which is often diagnosed at a pre-cirrhotic stage, since the GBD<sup>1</sup> database does not discriminate it. However, one meta-analysis, combining data from 2000 to 2015, pointed out an estimated prevalence of NAFLD in Europe of 23.71% (95% CI 16.12 to 33.45%).<sup>56</sup>

Again, NAFLD/NASH-related cirrhosis is not discriminated in data from the ELTR.<sup>7</sup> Since many cases of “cryptogenic cirrhosis” and “other cirrhosis” may be burned-out NASH, this would represent a percentage of up to 11.9% (8,427/71,007) of liver transplantations for cirrhosis from 1988 to 2016.

Given the drawbacks in obtaining reliable data on NAFLD/NASH prevalence, data may be mostly inferred from the prevalence of obesity and diabetes. There is evidence that for every 1 unit increase in BMI, the odds of NAFLD increase by 13% to 38% and per 1 cm increase in waist circumference, they increase by 3% to 10%.<sup>57</sup> It is also of note that excess body-weight is a significant co-factor for the progression of liver disease from all aetiologies.<sup>58</sup>

### Trends in obesity and type 2 diabetes in Europe

An upwards shift in population BMI has been observed in males and females across all regions in Europe. The majority of the data collected came from self-reported sources (only four countries had measured data), which are likely to be under-reported and therefore underestimate obesity prevalence.<sup>59,60</sup> Nevertheless, the increase



**Fig. 7. Time trends in age-standardised mortality from NAFLD/NASH – both genders by region.** (A) Northern, (B) Eastern, (C) Southern, (D) Western Europe.<sup>5</sup>



in obesity for countries in all regions is matched by the increase in NAFLD mortality, with a slight delay in peaks of obesity and peaks of NAFLD.

Regarding prevalence of obesity (BMI >30 kg/m<sup>2</sup>), a large variation among countries is observed, ranging from below 10% of the total adult population in Norway, Italy and Switzerland, to above 25% in Uzbekistan and the UK (Fig. 8).

Time trends from 2007 in the prevalence of adult type 2 diabetes in countries, by region, are shown (Fig. 9). Northern European countries showed a trend towards increasing prevalence of type 2 diabetes in adults, with some country exceptions. Similarly, for Eastern Europe, prevalence decreased between 2011 and 2013 in all countries apart from Slovenia and the Czech Republic, but all countries have experienced a recent increase between 2013 and 2015. In Southern Europe, prevalence was increasing for the majority of countries. Diabetes prevalence levels have generally remained stable in Western European countries, except for Germany where a sharp decrease followed by an increase was seen.

There are also large differences in the prevalence of type 2 diabetes across Europe. In 2015, <4% of the total population in European countries had type 2 diabetes, while in countries such as Serbia more than 10% of individuals were diagnosed with the condition (Fig. 10).

### Policies and interventions aimed at reducing obesity and diabetes

#### Interventions to reduce obesity

Given that obesity is a major risk factor for NAFLD and liver cancer, interventions that prevent or reduce obesity will have important impacts on subsequent incidence of obesity-related liver diseases. Obesity is a complex problem requiring multi-level and multi-sectorial action.<sup>61,62</sup> We summarised work by the WHO,<sup>63</sup> Harvard university,<sup>64</sup> the Heart Foundation Australia<sup>65</sup> and the UK National Institute for Health and Care Excellence (NICE).<sup>66</sup> These reviews assess the effectiveness and cost-effectiveness of a range of interventions to reduce childhood and/or adult obesity as well as other systematic reviews found in the academic literature.

#### Policy/population-level approaches

**Marketing of unhealthy foods and non-alcoholic beverages to children.** Marketing of food predominantly promotes the purchase of high fat, salt, and sugary foods,<sup>67</sup> given their long shelf life and cheap production.<sup>68</sup> In their review, the WHO concluded that the impact of limiting food and beverage advertising on television may be one of the most cost-effective public health approaches to reduce the prevalence of childhood obesity<sup>69,70</sup> and related NCDs.<sup>71</sup> The WHO framework for implementing the set of recommendations on the marketing of foods and non-alcoholic beverages

to children provides guidance on how to implement these recommendations.<sup>72</sup>

**Nutritional labelling – provision of nutritional information, in a standardised format, on foods sold.** Evidence suggests that nutritional labelling enables consumers to make healthier food choices.<sup>73</sup> Nutritional labelling that guides a consumer's understanding, in particular 'traffic light labelling' was cited by the WHO as a promising measure to tackle obesity. This labelling system uses colours (green, amber and red) to indicate the relative levels (low, medium or high) of fat, saturated fat, sugar and salt in the product. The labelling of calories on menus in fast food restaurants has also been identified as a promising obesity prevention measure.<sup>74</sup>

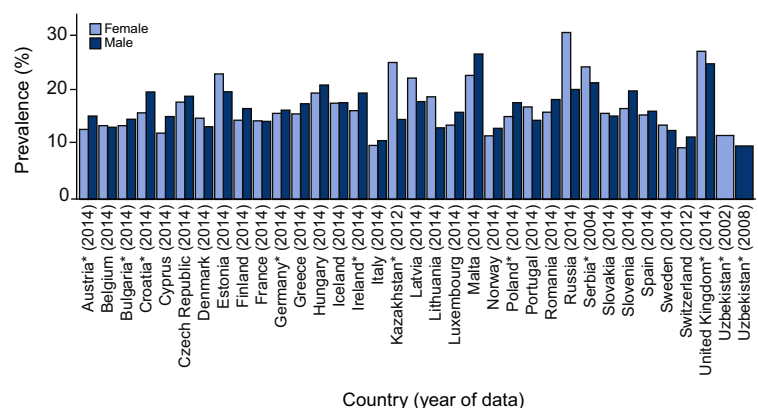
**Food taxes and subsidies.** There is strong evidence that price influences consumer patterns. Experimental studies have indicated that increasing price reduces purchase and subsequent energy intake.<sup>75,76</sup> The WHO carried out a meta-review of 11 recent systematic reviews on the effectiveness of fiscal policies to reduce weight, improve diet and prevent NCDs.<sup>77</sup> They concluded that the strongest evidence was for sugar-sweetened beverage (SSB) taxes, reducing consumption in the range of 20–50%. Fruit and vegetable subsidies increase consumption in the range of 10–30%, though evidence is mixed for their impact on BMI, net calorie intake and disease outcomes.

The UK Health Forum, in collaboration with Cancer Research UK modelled a 20% tax on SSB in the UK, estimated to prevent 3.7 million cases of obesity and 25,498 cases of BMI-related disease over the next 10 years (2015–2025), and avoid £10 million in National Health Service costs in 2025 alone.<sup>78</sup>

**Food reformulation.** Food reformulation is the reduction of salt and calories from sugar and saturated fat in processed foods or the increase

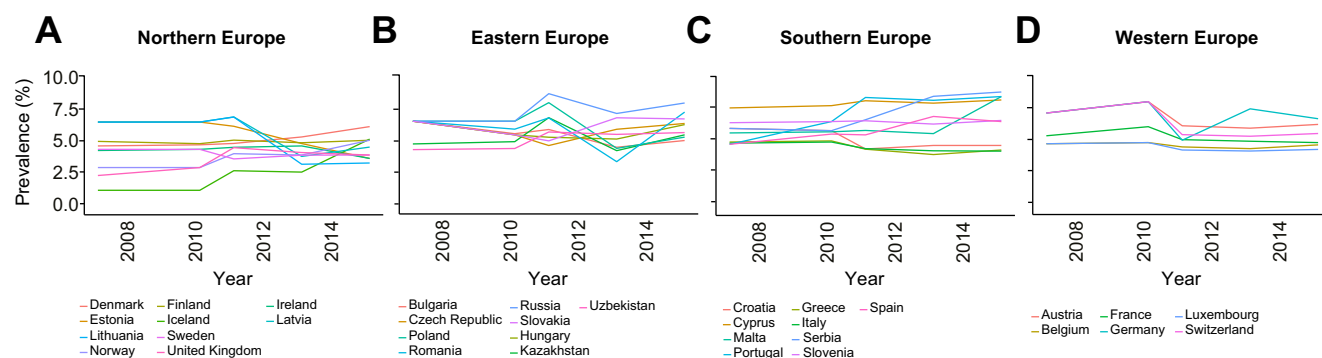
#### Key point

Obesity is a major risk factor for NAFLD and liver cancer, so interventions that prevent or reduce obesity will have an important impact on the subsequent incidence of liver disease.



Source: Range of national datasets

**Fig. 8. Prevalence of obesity (BMI >30 kg/m<sup>2</sup>) in females and males in the most recent year available.** Estimates come from measured BMI, all other data points used self-reported. Note: Uzbekistan estimates come from surveys in separate years and so are presented separately.



Source: International Diabetes Federation – Diabetes Atlas

**Fig. 9. Age-standardised national prevalence of type 2 diabetes in adults (both genders) aged 20–79 years over time by region.** (A) Northern, (B) Eastern, (C) Southern, (D) Western Europe. Estimation methodology was revised in 2011.<sup>13</sup>

of beneficial nutrients such as fibre, fruit, vegetables, and whole grains. These adjustments may be effective in reducing calories consumed and potentially reducing (or halting) rising obesity. However, a slow decrease (or increase) in nutrients is required to successfully shift population tastes.<sup>79</sup> Several studies explored the effectiveness of food reformulation as a strategy to improve population health and found that besides providing health benefits, such reformulation programmes have been shown to be cost-effective.<sup>80–82</sup>

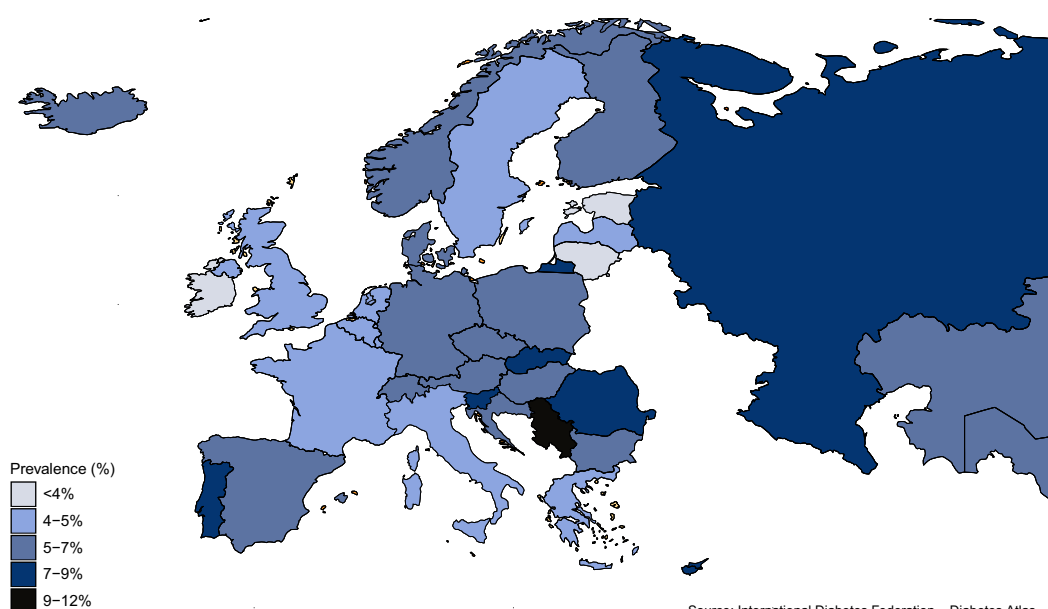
#### School-based interventions

Interventions in schools were found to have mixed results, according to Amini *et al.*<sup>83</sup> in their review of eight reviews on the impact of school-based interventions to control or reduce obesity. While multi-component interventions in a school setting were found to be the most promising approach for preventing obesity (*i.e.* consisting of diet, activity,

education/cognitive components), programmes that concentrate on single components (*e.g.* diet or physical activity) were sometimes effective in reducing adiposity measures.

#### Individual and family-based interventions

Both WHO and NICE recommend the use of multi-component lifestyle interventions, which typically include components such as diet, physical activity, and educational/cognitive.<sup>84,85</sup> One meta-analysis examined the clinical effectiveness of different types of interventions: diet or exercise alone vs. combined behavioural weight management programmes (BWMP).<sup>86</sup> They found only a significantly greater weight-loss in the combined BWMPs (−1.72 kg, 95% CI −2.80 to −0.64) at 12 months. In relation to childhood obesity, NICE found strong evidence from eight randomised controlled trials that child/adolescent and parent weight management interventions result in signif-



Source: International Diabetes Federation – Diabetes Atlas

**Fig. 10. Map of the age-adjusted prevalence of type 2 diabetes in adults, both genders (2015).**<sup>13</sup>

icant decreases in BMI, and are more favourable than child-only programmes.<sup>87</sup>

### Interventions to reduce type 2 diabetes and liver cancer

Type 2 diabetes accounts for 90–95% of all diabetes cases,<sup>88</sup> and the majority of patients with type 2 diabetes are obese and/or have high abdominal body fat. According to the International Diabetes Federation, 80% of type 2 diabetes cases are preventable with a healthy diet and physical activity.<sup>89</sup>

The diabetes prevention programme (DPP)<sup>90</sup> has been well evaluated and implemented in a number of countries. The initial randomised controlled trial<sup>91</sup> found that receiving a lifestyle intervention was more effective than metformin or placebo in decreasing the risk of developing type 2 diabetes (58% vs. 31% vs. 11%).

The role of metformin in diabetes has been investigated in relation to its impact on liver cancer mortality yielding mixed results, with some studies suggesting that metformin reduced the risk of liver cancer in type 2 diabetic patients<sup>92–95</sup> while others<sup>96–99</sup> found no significant impact of metformin on the risk of liver cancer, as recently reviewed by Fujita *et al.* (2016).<sup>100</sup> A recent meta-analysis, found diabetic metformin users have a 76% lower risk of hepatocellular carcinoma (HCC) than non-users.<sup>101</sup>

### Interventions to reduce NAFLD

Since obesity is a key risk factor for NAFLD, the aforementioned interventions, if successful, might be assumed to have an impact on the subsequent reduction in NAFLD. However, on a population basis, the impact of successful obesity interventions on reducing NAFLD prevalence will be a slow process. A study from Vreman *et al.*<sup>102</sup> using a microsimulation model with Markov chains for NAFLD (including steatosis, NASH, cirrhosis and HCC) estimated that a 20% reduction in added sugar consumption is projected to annually avert 0.767 million (M) disability-adjusted life years (95% CI 0.757 M to 0.777 M) and a total of US\$ 10.3 billion (B) (95% CI 10.2 B to 10.4 B).

## Viral hepatitis-related liver disease

### Current prevalence of hepatitis B virus and historic trends

Estimates of population hepatitis B virus (HBV) prevalence are limited by the lack of high-quality, representative nationwide prevalence estimates, especially in younger age groups.

Two of the most comprehensive studies into national-level prevalence estimates of chronic HBV infection in the general European population provided inconsistent results.<sup>103,104</sup> However, both showed regional variation with higher rates in Eastern and Southern European countries compared to Northern and Western European

countries.<sup>103–105</sup> These prevalence estimates in both reviews are likely to be an underestimation (in part due to inclusion of estimates among blood donors as a proxy for the general population in the absence of other evidence). These two datasets were compared to the modelled estimates of hepatitis B surface antigen (HBsAg) prevalence from the Polaris Observatory<sup>10,106</sup> and showed that HBsAg prevalence was fairly stable or slightly decreasing in Northern Europe between 2007 and 2017, with prevalence below 1.5%. Southern and Western Europe showed decreasing trends (<2% and 1% HBsAg prevalence, respectively), while Eastern Europe had stable or decreasing trends with less than 5% HBsAg prevalence (Uzbekistan had <10% prevalence in 2007 and <8% prevalence in 2017). Overall, estimates indicate that approximately 15 million people are living with HBV in the EU.

A time-trend analysis of the WHO seroprevalence showed HBV prevalence decreasing globally, but trends varied between countries in Europe:<sup>107</sup> HBsAg prevalence increased over time in Poland and Russia, potentially as a consequence of strong political and social changes since 1963, resulting in increased access to injectable drugs. Historically low endemicity countries, such as France, Germany and Spain, showed little reduction over time, while other countries have seen large annual reductions (>5% annual change), for instance the UK, Greece and Slovenia where trends mirror those of high income Eastern Mediterranean states. A fourth group of countries are those with medium to low endemicity, with a relative decrease of around 5% per year.

Variation in HBV prevalence between countries can be partly explained by vaccination policies, although the majority of data shown is in adults, so it is not clear if there has been a shift in mean age at infection after the implementation of hepatitis B vaccination in some countries in the late 1990s. Other factors that could explain the changes include improvements in infection control (blood donation screening, medical settings prevention, health worker vaccination, awareness and health promotion around disease and transmission) and changes in hepatitis B case reporting. More focussed assessment of the prevalence of hepatitis B exists for specific risk groups, in particular PWID, may reveal differences in hepatitis B prevalence across European countries.

### Current prevalence of HCV and historic trends

Estimates of HCV prevalence from representative anti-HCV surveys<sup>103</sup> were available for the general population for 13 countries in a recent ECDC review, ranging from 0.1% (Belgium, Ireland and the Netherlands) to 5.9% (Italy). A recent global estimation of HCV prevalence of 1.8% in Europe, suggests over 13 million estimated cases.<sup>108</sup> Overall, the Polaris estimates seem lower than previously published data. For the EU, approxi-

### Key point

Overall estimates indicate that approximately 15 million people living in the EU are infected with HBV.

mately 3.2 million people have viraemic HCV infections.<sup>109</sup> However, non-EU countries considered in the present report contribute an additional 6.0 million patients with viraemic hepatitis C.<sup>9</sup>

#### Interpretation of hepatitis B and C data

Interpretation of both hepatitis B and C data is difficult, as trends are likely a reflection of both testing and screening practices. The mix of acute and chronic cases, the lack of availability of good quality, timely and nationally-representative, general-population level data are limitations to the use of hepatitis B and C incidence and prevalence data. The lack of gender and age-stratified data makes it difficult to evaluate the impact of hepatitis B vaccination policies and practices. Surveillance systems are heterogeneous, coverage varies, and several case definitions are used for both hepatitis B and C. More robust prevalence estimates are needed for the general population in countries and in specific risk groups.

#### HBV and HCV-related liver disease burden

The 2017 WHO Global hepatitis report<sup>110</sup> states that HBV and HCV infections account for 96% of the global mortality from hepatitis-related end-stage liver disease.

Although the majority of prevalent cases of cirrhosis and other chronic liver diseases are accounted for by alcohol use and HBV and HCV infections in the GBD,<sup>1</sup> countries vary in the relative contributions of these aetiologies. Thus, in many Western countries (such as Ireland, Germany and Portugal), where alcohol is the most important risk factor, viral hepatitis B and C combined contribute to a lesser extent, while a smaller proportion of cirrhosis and liver disease cases are due to other undefined causes. In Central European countries however, viral hepatitis and alcohol contribute approximately equally to the burden of liver disease. Viral hepatitis is the main determinant of disease for all ages and genders when considering countries further east. In Eastern Europe, HCV generally accounts for a greater proportion of liver disease cases than HBV, however in Kazakhstan and Uzbekistan hepatitis B accounts for more cases than hepatitis C (see HEPAHEALTH report).

The GBD<sup>1</sup> shows a north-south gradient in the modelled data of HCC – with the highest rates being reported for Italy (see main HEPAHEALTH report). Viral hepatitis was the predominant aetiology, followed by alcohol use, with the exception of Sweden, where non-viral, non-alcohol-related aetiologies accounted for the majority of HCC cases. HCC cases associated with HBV infection were more prevalent in Eastern European countries, whereas HCV was more frequent in Western European and Mediterranean countries.

Viral hepatitis mortality seems to play a minor role in overall liver-related mortality. Alcohol is the most important determining factor in most

countries, with the exception of Italy, where viral hepatitis predominates. However, a significant proportion of deaths due to unknown factors or HCC, raise the question about the completeness of death certificates. A recent linkage study from Switzerland estimated under-reporting of HCV infection in up to 45% of death certificates among deaths from HCV-related complications,<sup>111</sup> while a US study reported even higher rates of under-reporting.<sup>112</sup> Viral hepatitis leads to HCC, and this might instead be the cause of death recorded, among other complications such as sepsis, encephalopathy or digestive bleeding.

#### Historic trends of HBV- and HCV-related morbidity and mortality

While the increase in prevalence of end-stage liver disease in Northern and Eastern Europe seems significantly driven by increased alcohol use, time trends observed in Western and Southern European countries underline a major role of HBV and HCV infections. HBV and HCV, together with alcohol, account for a major proportion of liver cancers in Northern and Western European countries. The modest increase observed in Russia is driven mostly by alcohol use (the other aetiologies remaining almost unmodified over time), while the HCC increases in Southern Europe were largely due to increases in liver disease caused by hepatitis B and especially hepatitis C.

Regarding mortality, viral hepatitis remains a high priority throughout Europe. Increases were observed in most Northern European countries, Hungary, Italy, Croatia, and Portugal (see main HEPAHEALTH report), whereas in the remaining countries (such as France and Germany), rates have remained stable or even decreased slightly over time. This is possibly related to the high antiviral treatment uptake reported for those countries.<sup>113</sup>

#### Interventions for the prevention and treatment of chronic viral hepatitis B and C

The global burden of viral hepatitis has been highlighted by the WHO with activities such as the publication of the first guidelines for the prevention, care and treatment of persons living with chronic hepatitis B infection<sup>114</sup> and guidelines on the screening, care and treatment of persons infected with hepatitis C<sup>77</sup> (to be updated in 2018), as well as the World Health Assembly (WHA)'s endorsement of the Global Health Sector Strategy on viral hepatitis 2016–2021.<sup>115</sup> This strategy aims at reducing new HBV and HCV infections by 90% and mortality by 65%. The baseline situation detailed in the WHO report<sup>116</sup> and elsewhere<sup>109</sup> shows how the European region is well positioned to easily reach most of its goals, with the notable exception of effective testing strategies and treatment, where more aggressive policies are needed.

#### Key point

As a significant cause of mortality, viral hepatitis remains a high priority throughout Europe.



*Prevention through vaccination*

HBV vaccination of newborns or adults at high risk is effective in preventing long-term chronic HBV infection,<sup>117</sup> and cost-effective regardless of endemicity.<sup>118,119</sup> As of August 2017, all countries in the HEPAHEALTH project include hepatitis B vaccination as part of their vaccination schedule, with the UK being the last EU country to introduce it.

An effective HCV vaccine is not currently available. Despite HCV vaccine development efforts being hampered by several immune evasion strategies,<sup>120</sup> several vaccines are currently being developed, and a few are in human studies.<sup>121,122</sup>

The current costs of direct-acting antivirals (DAAs), compared to traditional vaccination costs, make HCV vaccination a much cheaper transmission control strategy: a recent modelling study in the UK<sup>123</sup> estimated that even low efficacy HCV vaccines would have considerable impact on prevalence and incidence among PWID over 40 years. They found that similar reductions in prevalence or incidence could be achieved with 4–16 or 2–11 times fewer HCV treatments, respectively.

*Improvement in access to testing and diagnosis of hepatitis B and C*

The cost-effectiveness of screening the general population for viral hepatitis is a matter of debate, and affected primarily by the high cost of DAAs (in the case of HCV) and the rate of referral (notoriously poor for both viruses). A 2013 systematic review of the cost-effectiveness of HBV and/or HCV screening included 29 publications with varying eligible populations and implementation of screening.<sup>124</sup> Overall, HBsAg screening of the baby-boomer generation, universal HBsAg antenatal screening, HBsAg screening of migrants, HCV screening and treatment of the general population and in PWID were found to be cost-effective. There was limited evidence on the effectiveness of HCV antenatal screening, or screening of migrants, prisoners, men having sex with men (MSM), or sexual health clinic attendees in the UK. Strategies to increase the cost-effectiveness of screening for viral hepatitis include: targeting birth cohorts,<sup>125–128</sup> or using point-of-care assays followed by nucleic acid testing performed reflexively.<sup>129,130</sup> In countries where a high prevalence of infection is associated with widespread use of low-cost generic DAAs, these hurdles are easily overcome, allowing for generalised screening.<sup>131</sup> No consensus currently exists as to the optimal screening strategy. Data on access to and uptake of DAAs was only available for a selection of European countries.<sup>132</sup> There are persisting, significant variations in access of patients to DAAs across European countries: by January 2017, Portugal, Belgium and Germany have now treated over a quarter of their patients estimated to be infected. By contrast, the trend in the UK has been one of slower and lower levels of access.

*Harm reduction*

Among PWID, sharing needles/syringes and other paraphernalia is the main risk factor for HCV infection. Needle syringe exchange programmes (NSP) provide clean syringes and needles to prevent onward transmission. They operate through fixed sites, outreach, peer PWID networks, vending machines and pharmacies, and include opioid substitution therapy (OST), psychosocial approaches and residential rehabilitation. In a systematic review,<sup>133</sup> OST reduced HCV incidence by between 32% and 73% in European countries, with little variation due to study design considerations and by 74% (95% CI 11–93), when combined with high coverage of NSP. This confirmed findings of large protective effects of NSP and OST on injecting risk behaviours associated with blood-borne viral transmission.<sup>134</sup> However, another systematic review found limited evidence of an effect.<sup>135</sup> A modelling study predicted that scaling up OST and NSP combined with antiviral therapy, *i.e.* by applying the concept of treatment as prevention would reduce incidence and prevalence of HCV among PWID.<sup>90,136</sup>

Variation in findings may be due to limitations intrinsic to NSP programmes: the need for a large number of syringes per user per year, the increased survival of HCV in injection paraphernalia compared to other blood-borne pathogens, and the fact that HCV infections often occur early in the injection career, before injectors get into contact with appropriate services.<sup>137,138</sup>

A modelling study has predicted that significantly reducing both incidence and prevalence of HCV among PWID could only be achieved by scaling up OST and NSP combined with antiviral therapy, *i.e.* by applying the concept of treatment as prevention,<sup>90,136</sup> given that a sustained virological response (SVR) is tantamount to clearance in the vast majority of people, even among high-risk populations. Although sexual transmission of HCV is infrequent among monogamous, serodiscordant couples,<sup>139</sup> a high transmission rate has been recently reported among MSM engaged in high-risk sexual practices.<sup>140</sup> Risk factors for transmission of HCV among MSM are coinfection with HIV<sup>140</sup> and sexualised drug use (“chemsex”).<sup>141</sup> HIV-negative MSM may become infected with HCV if engaged in high-risk sexual practices.<sup>142</sup> Strategies aimed to eliminate HCV in HIV-positive MSM should include aggressive awareness campaigns to promote the correct and consistent use of condoms, and, possibly, the implementation of a treatment as a prevention approach.<sup>143</sup> However, a modelling study has pointed out how reducing high-risk sexual behaviour would be the most effective intervention for controlling the HCV epidemic among MSM, independent of treatment interventions.



### Achieving the WHO targets in Europe for HBV and HCV

A simulation model of the global HBV epidemic was recently developed,<sup>116</sup> Western European countries would be capable of reducing HBV-related mortality below a threshold of 50 deaths per 100,000 by the early 2020s with comparatively small interventions (essentially increasing the treatment uptake to 80%), while Central and Eastern Europe may reach the same goal before 2030.

For HCV, another modelling study estimated the level of intervention required to achieve WHO targets of 65% reduction in liver-related deaths, a 90% reduction of new viral hepatitis infections, and 90% of patients with viral hepatitis infections being diagnosed by 2030.<sup>109</sup> Their model suggests that to achieve the WHO targets, treatment would need to increase from 150,000 patients annually using DAAs at 95% SVR in 2015 to 187,000 in 2025, with expansion of treatment age to 15–74 years old, and treatment of all fibrosis stages. Screening should also be expanded from 88,800 new cases annually in 2015 to 180,000 by 2025. EASL clinical practice guidelines currently recommend that all patients with HCV infection should be considered for treatment.<sup>144</sup>

### Discussion and interpretation

#### Liver disease epidemiology is changing and can be changed

Evidence gathered across this study presents liver disease as a complex, diverse and important disease in Europe. Very significant shifts in liver mortality have occurred since 1970. There have been up to fourfold decreases in Southern European countries as a result of decreased wine consumption. In other countries there have been increases in liver mortality of equal magnitude. Experience from earlier in the 20th century illustrates how rapidly liver mortality can change in response to the factors that influence behaviour at a population level, despite the fact that it takes between 10 and 50 years of progressive fibrosis to develop cirrhosis, liver failure and HCC. The rationing of alcohol during warfare, prohibition in the US or Gorbachov's 1980s policy in the Soviet Union led to dramatic changes in liver mortality within a few years, with the maximum changes occurring within five years.<sup>22,145</sup> The explanation for this paradox probably lies in the fact that much of the mortality from alcohol-related liver disease is a result of acute-on-chronic liver failure related to recent drinking.

HBV and HCV are important drivers of liver disease, and may be the most important driver in certain countries. Rising prevalence of obesity throughout the vast majority of Europe is likely to further shift the distribution of the burden of liver disease, and in some countries, is already a significant cause of cirrhosis and HCC. These risk

factors are synergistic, for example a BMI greater than 35 kg/m<sup>2</sup> doubles the hepatotoxicity of alcohol.<sup>17,146</sup> Similarly an alcohol intake of more than 17.5 cl per week can increase the mortality of hepatitis C by 2.5 times.<sup>147</sup> Therefore, it is probably unhelpful to think of liver disease within independent disease silos, but to consider liver disease at a population level as the outcome of a multifactorial process, with an important role for health inequality.<sup>148</sup>

#### Strategies for reducing the risk factor for liver disease exist

Several strands of evidence, from empirical, epidemiological and modelling work have shown the potential for reducing the principal risk factors for liver disease within a population. These strategies will vary in administrative cost and impact, depending on the risk factor in question, a country's epidemiology and the context in which they are implemented, but they can be broadly categorised into population and individual-level approaches.

For alcohol the most effective and cost-effective intervention is to increase the price of alcohol.<sup>15,20</sup> This measure has the additional advantage that it increases treasury revenues, thus increasing the capacity of health systems to tackle the adverse impacts of alcohol misuse. There is a wealth of evidence that alcohol marketing has a deleterious impact on young people.<sup>45</sup> Modelling studies suggest that marketing regulations would be effective and cost-effective.<sup>149</sup> Evidence from natural experiments is ever increasing, with the French Loi Evin as an excellent example of practical and effective regulation of alcohol marketing.<sup>149,150</sup> India and Russia have banned alcohol advertising, joined most recently by Lithuania. Policies regulating the availability, the marketing of alcohol and the drink environment and availability of alcohol have been identified, as well as screening and brief interventions and alcohol treatment.

Several policy options have been examined with the aim of reducing obesity and diabetes, with recommendations including adjusting the food environment through regulation of marketing to children, improvement of nutritional labelling and reformulation, fiscal measures, such as the (now defunct) Danish tax on saturated fat,<sup>151</sup> the UK's upcoming levy on SSBs<sup>152</sup> or Hungary's 2011 "chips tax" on food high in salt, sugar or caffeine,<sup>153</sup> as well as subsidies to dissuade consumption of harmful commodities or persuade consumption of healthy commodities. Individual-level interventions to increase physical activity, or reduce obesity through behavioural lifestyle interventions were also noted as likely to reduce obesity rates in specific population groups.

The European region is uniquely positioned to achieve the WHO target of elimination of viral hepatitis as a public health threat by 2030.<sup>154</sup>

#### Key point

Historical experience illustrates how rapidly trends in liver disease mortality can change in response to population-level factors.

Vaccination against HBV, DAAs for HCV, increased testing for both HCV and HBV and harm reduction through needle-exchange and OST are likely to reduce the burden of viral hepatitis infection in both general and high-risk population groups. Commitment to integrated action of multiple interventions across the spectrum of the varied epidemiological, demographic and socio-political landscape of Europe is key to any successful elimination of hepatitis. Indeed, screening for hepatitis C in the general population in the US was estimated to be cost-effective and reducing HCV-related morbidity and mortality, but the authors noted that this effectiveness would be contingent on improved rates of referral, treatment, and cure.<sup>155</sup>

Extending screening for other chronic diseases to reduce late diagnosis is also likely to have a large impact on mortality, as screening helps to identify patients at genetic risk of alcoholic or other liver diseases; can prompt behaviour change (abstinence, weight control) and form the basis for further screening programmes to prevent life-threatening complications.

### Challenges and potential limitations

One of the factors that can enhance the effort to reduce liver disease is the relevant, timely, standardised data collection for programmatic monitoring and evaluation. The data used for this study was extracted from standardised databases, in order to increase comparability between countries and across time for historical trends. This reduced the granularity of the data available, as definitions and categorisation of diseases available in international databases (i.e. WHO and GBD) were far broader than clinical classifications traditionally used. Nevertheless, using this standardised data avoided the complications arising from countries' different use of terminology, diagnosis, data recording and reporting practices, which creates uncertainty when comparing national-level data, or historical data. While the European-level perspective of the project included a large number of countries, not all countries were included because of time and resource limitations. Thus, data and trends in some Eastern and Central Asian countries were not explored. Although the reviews focussed on upstream drivers of liver diseases, infection with hepatitis virus, obesity and harmful alcohol use, this review did not cover other rarer origins of liver disease (i.e. genetics, drug use) in any detail. However, the focus on determinants that can be modified or reduced through health policies provides some concrete options for national and international policy makers to tackle the rising burden of liver disease in Europe.

While previous reports and analyses also described the burden of liver disease in Europe, we did not restrict the focus to one risk factor, and included historical trend data in order to provide more information on the context in which

policies need to be implemented for different countries. The international focus also allows situations between countries to be compared, but can help policy makers identify evidence and experience from culturally, politically and epidemiologically similar European neighbours. The initial review describing the burden of the liver disease across Europe, coupled with trends in risk factors, serve to illustrate the magnitude of the problem, and hopefully, identify liver disease as an important priority for European policy makers, clinicians and health researchers.

Even for a developed region such as Europe we have noted throughout that epidemiological data on the burden of liver disease is in many areas of insufficient quality, comparability and relevance.

Therefore, this work serves as a call to action on surveillance and data collection of analysis on liver disease, highlighting that further work is needed in collecting, harmonising, defining and reporting data. While no specific Europe wide guidelines exist on the collection of liver disease surveillance data, any plan to enhance surveillance of liver disease in Europe should incorporate elements of continuity (data collection should be ongoing); practicality (implementation should be feasible, but also should be useful for onwards action); uniformity (standardisation of notifications, and reporting practices within and across countries); and should be timely to allow prompt programmatic action. Based on mortality data reported to international organisations, more work needs to be done to clarify and codify the aetiology and causes of death. One prime example of this is in NAFLD/NASH, which is under-represented in the causes of death and in the proportion of prevalent cases of liver disease, in part because of historical coding and data collection. Future efforts to elaborate ICD-10 and other codes for liver disease should consider the current picture of the disease.

### Conclusions

The progressing and increasing profile of liver disease in Europe is a concerning issue. The uncertainties in the sources of data do not detract from the overall picture of liver disease as a growing public health problem across Europe. This study highlights that the governance and public health tools to reverse this trend exist. These tools should be implemented and integrated to have a timely and significant impact on liver disease morbidity and mortality. The time for action is now.

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### Conflict of interest

Helena Cortez-Pinto received lecture and advisory board fees from Intercept, Genfit, and Gilead.

Francesco Negro received a research grant from Gilead and AbbVie, and is advising Gilead, AbbVie, and Merck. Jeffrey Lazarus declares speaker fees and research grants from AbbVie, Gilead Sciences and MSD, outside of this study. The other authors declare no conflict of interest.

Please refer to the accompanying [ICMJE disclosure](#) forms for further details.

### Authors' contributions

Laura Pimpin was responsible for the overall management of the project, analysed data, designed and consolidated the scope, led the review of the literature, conducted qualitative interviews, and drafted the final report. Helena Cortez-Pinto advised on the HEPHEALTH project and drafted the obesity/type 2 diabetes and liver disease section of the manuscript. Francesco Negro advised on the HEPHEALTH project and drafted the viral hepatitis section of the manuscript. Emily Corbould collected, collated and analysed data, participated in the review of the literature and contributed to the write-up of the report. Jeffrey

V Lazarus advised on the HEPHEALTH project and revised the full manuscript. Laura Webber advised on the design of the project, conducted qualitative interviews, participated in the review of the literature and contributed to the write-up of the report. Nick Sheron advised on the HEPHEALTH project and drafted the introduction, Alcohol and liver disease, and discussion sections of the manuscript.

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### Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.jhep.2018.05.011>.

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