HEPAHEALTH Project Report

November 2017

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Overall Report

The report was drafted by a team at UK Health Forum under a grant from EASL in 2017. 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.

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SUMMARY

The aims of the HEPAHEALTH project were:

- to report the latest data on the epidemiological burden of liver disease in 35 European countries and historical trends
- to present data on the main risk factors for liver disease
- to carry out a 'review of reviews' that have appraised public health interventions or policies aimed at preventing or reducing the burden of liver disease through the reduction of the risk factor in the population.

Data were collected and analysed from a range of sources, including peer reviewed and grey literature reviews, and representative international databases. A qualitative study of European liver disease experts on liver disease and risk factor trends as well as policy priorities was also conducted to enrich the data, provide context and triangulate our understanding of liver disease more fully

Part 1: The current and historical burden of liver disease in Europe

Data show that the European region has some of the higher rates of liver disease mortality globally.

Prevalence of compensated and decompensated cirrhosis and other chronic liver diseases modelled by the Global Burden of Diseases project ranged between 500 and more than 1,100 cases per 100,000, the majority of which were caused by alcohol use and hepatitis C infection. However, the relative contribution of these risk factors to cirrhosis prevalence rates varied between countries: in Western and Northern European countries, alcohol was the most important contributor, while in Southern and Eastern European countries, hepatitis; in particular hepatitis C virus was the main cause of cirrhosis cases. Modelled prevalence rates of liver cancer varied between <2 to 12 cases per 100,000, with hepatitis B and C as the predominant contributors, although alcohol and other causes emerged as important in some cases of liver cancer, in particular in Northern European countries.

Age-adjusted mortality from all-cause liver disease obtained from the World Health Organization's raw mortality data ranged between 10 to 36 deaths per 100,000 across European countries, and these deaths were attributable to a range of aetiologies. Alcoholic liver disease and cancer were important causes of death, there were relatively small numbers of deaths attributed to viral hepatitis, and deaths from fatty liver disease were emerging in a small number of countries, in the most recent years. One important consideration is that liver disease from unknown aetiologies constituted a large proportion of all deaths reported, and this may be a source of bias in estimating the true distribution of aetiology of liver disease mortality in Europe. Interestingly, on average two thirds of all potential years of life lost due to mortality from liver diseases were working years of life. This is in contrast to the majority of potential years of life lost from other chronic disease, for instance stroke, as the majority of stroke deaths occur later on in life.

Countries can be classified into different historical patterns of mortality from cirrhosis and other chronic liver diseases as shown in Figure 1:

- **Decreasing trends:** rates have dramatically decreased from very high rates in 1970s
- **Increasing trends:** rates have seen a sharp increase over 45 years
- **Low stable trends:** rates remaining consistently below ~ 20 deaths per 100,000
- **High stable trends:** rates remaining consistently above ~ 20 deaths per 100,000

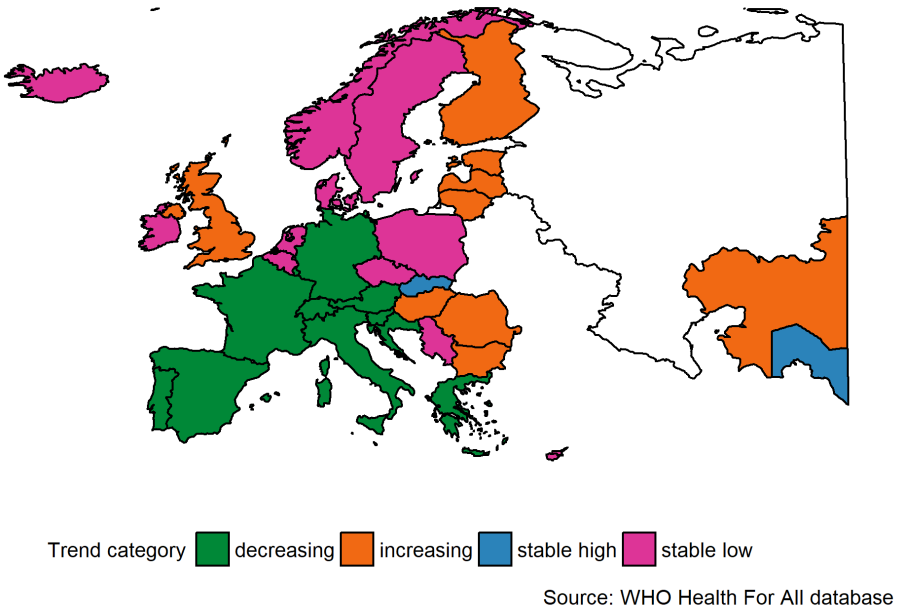

Figure 1.Map of time trend in age-adjusted mortality from cirrhosis and other chronic liver diseases between 1970 and 2016
(Luxembourg: decreasing; Malta: increasing)

Liver cancer mortality has increased for the majority of European countries, with only a few having experienced decreases, or stabilisation of rates since 1980. This matches the modelled historical increase in prevalence of liver cancer over recent years from the Global Burden of Diseases project. Data on the population-level prevalence of chronic hepatitis B and C infections is sparse, and data collection is limited by the concentration of prevalence in various hard to reach risk groups. Summarising both survey sources and modelled estimates, prevalence of chronic hepatitis B infection ranged from less than 0.5% to 8% in European countries, with higher prevalence concentrated in Southern and Eastern European countries. Limited evidence in historical trends suggest that there has been a steady decrease in hepatitis B prevalence overall in the last 30 years, but some countries appear to differ in this trend, as they have seen a recent increase in hepatitis B infection, for instance Poland and Russia. Evidence on the population prevalence of chronic hepatitis C infection is also limited, in part due to the concentration of infection in risk groups, such as people who inject drugs.

The trends in prevalence and mortality of different liver diseases across European countries must be interpreted with caution. Prevalence estimates are likely to be affected by the model used, the quality of input data that the model is based on, as well as source-specific bias in

reporting the prevalence. Mortality data, in particular the distribution of various categories of liver disease mortality, must also be interpreted within context. Using primary cause of death ICD-10 coding is likely to underestimate liver disease mortality, as it may not be the reported cause of death in multi-morbid cases. Furthermore, countries may vary in the codes used to allocate mortality; the proportion of liver disease deaths classified as unknown varies greatly between countries, and more precise and standardised coding strategies may increase the precision of liver mortality estimates.

Part 2: Trends in risk factors for liver disease in Europe

Liver disease can be caused by a range of factors, some of which can be modified (environmental causes) while others are largely due to immune or genetic factors. The focus of the second section of this review was on modifiable risk factors for liver disease which offered opportunities for intervention. A deeper understanding of the trends in these behavioural risk factors could offer some insight into current epidemiological trends in liver disease, as well as information on future interventions and policies. Alcohol use, obesity and type 2 diabetes prevalence, as well as hepatitis B and C infection were identified as the main upstream, behavioural risk factors for liver disease in the European populations.

Alcohol consumption in the European continent is the highest globally, but patterns of and trends in consumption varied largely across countries. Alcohol consumption has dramatically decreased in some countries, predominantly in Western and Southern Europe. These countries, where the type of alcohol consumed has also often shifted to more beer and less wine or spirit drinks, tended to be those in which mortality rates for cirrhosis and other chronic liver diseases have decreased over recent decades (see Figure 1). Conversely, in countries such as Estonia, Finland and the United Kingdom, where mortality rates have been increasing over time, alcohol consumption has also increased. While ecological correlation is no proof of causation, it does suggest that a countries' historical and current alcohol consumption trends may go a long way to explaining patterns in cirrhosis mortality.

Obesity and type 2 diabetes rates have increased in the vast majority of countries in Europe, with any decreasing trends likely to be artefacts in reporting, data definitions or changes in methodology. The increasing trend for excess weight across European countries maps well onto the emerging increases in mortality from non-alcoholic fatty liver disease, as well as increases in cancer mortality across European countries.

Hepatitis B and C infection are themselves liver diseases, but are also risk factors for other chronic liver diseases, in particular liver cancer. One of the important routes of hepatitis B and C viral infection in European countries is the use of injectable drugs. The prevalence of hepatitis C for instance, is up to 50 times higher in people who inject drugs, compared to the general population, in European countries where data are available. Data on the risk behaviours are limited for many countries, but prevalence of injection drug use ranged from 0.02% in Spain to 0.92% in Latvia. Variations in the prevalence of the use of injecting drugs in part explain variations in hepatitis B and C prevalence in the general population, though accurate estimation of prevalence is limited by a range of biological, demographic and surveillance factors.

Qualitative expert interviews

Seven experts were interviewed using a semi-structured questionnaire, while another seven country representatives for liver disease were also interviewed in a group discussion setting.

Respondents discussed how trends in liver disease had changed in their respective countries over time; the observation from prevalence and mortality data that aetiologies were shifting to alcohol and obesity in Western and Northern countries, while viral hepatitis remained the focus in some Eastern and Southern European countries was mirrored in the expert interviews. The respondents identified the main risk factors reviewed in part 2 of the report (alcohol, obesity and viral hepatitis) as the main barriers to good liver health, but also highlighted the role of limitations in medical systems capacity, training, screening and diagnostic ability, issues related to funding and lack of governmental policy to prevent liver disease. Treatment and policy action, diversifying liver disease expertise and improving public awareness of the disease were highlighted as the priorities in combatting liver disease in Europe.

Part 3: Policies and interventions aimed at reducing the risk factors for liver disease

A range of organisations have reviewed the evidence for interventions and policies aimed at reducing population-level exposure to alcohol, obesity and type 2 diabetes, and hepatitis B and C infection.

There is a large body of evidence on the policy options for reducing population-level alcohol consumption, including fiscal policies (minimum unit pricing, tax and duty increases), strategies to restrict the marketing of alcoholic products especially to younger populations, restricting the temporal and spatial availability of alcoholic products, as well as screening of abusive alcohol consumption in patient populations.

Strategies to reduce the population-mean body mass index (or by extension, the prevalence of obesity) as well as the prevalence of type 2 diabetes can also be classified into categories similar to those of alcohol interventions. Namely, fiscal policies such as taxes, subsidies for healthy foods, restricting marketing, in particular of unhealthy foods to children, reformulation of food products, as well as public information in the form of provision of nutrition information, in a standardised format, on foods sold, social marketing and individual and community level weight loss interventions.

Hepatitis B and C are considered to be liver diseases, but also risk factors for other liver diseases. The main infection control intervention and policies to reduce the risk of onwards transmission of chronic viral hepatitis (B and C) include developing and promoting screening for infection, and treatment. Expanding access to treatment for hepatitis C, with the new direct-acting antivirals that have superior viral clearance rates is likely to contribute to the reduction of transmission, although this effect has yet to be assessed at population level. Hepatitis B vaccination of eligible populations (largely neonatal in Europe) and interventions to reduce harm for people who inject drugs and sexual transmission in men who have sex with men are established infection control strategies for blood-borne viruses, and efforts must be continued and expanded. In particular, monitoring and evaluation of programmes should be developed, to inform on the cost-effectiveness of these interventions and allow prioritisation of resources.

There was limited evidence as to the effectiveness and cost-effectiveness of programmes aimed at screening populations, or targeted population subgroups, for liver diseases.

Identifying and diagnosing individuals with auto-immune, metabolic, paediatric and genetic liver diseases to provide earlier and potentially more effective treatment should contribute to reducing the burden of liver disease. Population level screening for more common liver diseases (alcoholic and non-alcoholic fatty liver disease) may also reduce the burden of liver disease through the identification of risk behaviours. However, evidence on this topic is limited, and further research should be conducted into how such programmes should be implemented.

Findings from this project have highlighted the heterogeneous nature of liver disease: geographically diverse pattern in the prevalence and mortality of disease, as well as in the upstream risk factors mean that reducing the burden of disease across all European countries and all aetiologies will be challenging.

Nevertheless, the variety of risk factors for the different types of liver disease offer a range of targets for public health, population-level interventions: reducing alcohol consumption especially within the heavy drinkers subgroup, effecting change to reduce the prevalence of obesity and diabetes type 2 at population level, as well as reducing the transmission of hepatitis B and C among high risk population groups are likely to have significant impacts on the burden of liver disease. These interventions range from top-down policies, to more individual-level prevention efforts. The multifactorial nature of liver disease means that simply tackling one risk factor or even one strategy for tackling one upstream determinant of liver disease will not be enough. A concerted, integrated and multi-sectorial effort will be required to implement the most effective and cost-effective strategies aimed at reducing risk factors such as alcohol, obesity and viral hepatitis, at both population and individual level. Reducing the exposure of populations, especially at risk groups, to unhealthy commodities such as alcohol, unhealthy food, and injection drug use, as well as improving access to earlier diagnosis and testing for liver disease will likely impact on the growing burden of liver disease in Europe.

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ABBREVIATION LIST

Abbreviation	Definition
95%CI	95% Confidence Interval
AA	Alcohol Attributable (deaths)
AASLD	American Association for the Study of the Liver
APC	Age-Population-Cohort
ARM	Alcohol-Related Mortality
BMI	Body Mass Index
BWMP	Behavioural Weight Management Programs
DAA	Direct Acting Antiretroviral
DMDB	Detailed Mortality Database
DPP	Diabetes Prevention Programme
EASL	European Association for the Study of the Liver
ECDC	European Centre for Disease Prevention and Control
ELTR	European Liver Transplant Registry
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EU/EEA	European Union/ European Economic Area
GBD	Global Burden of Disease
GDP	Gross Domestic Product
GP	General Practitioner
HBsAg	Hepatitis B surface antigen
HIV	Human Immunodeficiency Virus
ICD-10	10th revision of the International Statistical Classification of Diseases and Related Health Problems
IDF	International Diabetes Federation
IHD	Ischemic Heart Disease
MCLI	Multi-Component Lifestyle Interventions
MSM	Men who have Sex with Men
MUP	Minimum Unit Pricing
NA	Nucleos(t)ide Analogues
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
NCD	Non-Communicable Disease
NICE	National Institute for Health and Care Excellence (United Kingdom)
NSP	Needle Syringe Programmes
OECD	Organisation for Economic Co-operation and Development
OST	Opioid Substitution Therapy
PWID	People Who Inject Drugs
PWYLL	Potential Working Years of Life Lost
PYLL	Potential Years of Life Lost
QOF	Quality Outcomes Framework
RCT	Randomised Controlled Trial
RR	Relative Risk

SES	Socio-Economic Status
SSB	Sugar Sweetened Beverages
SVR	Sustained Virological Response
VAT	Value Added Tax
VLED	Very Low Energy Diet
WHO	World Health Organization

Introduction

Liver disease is a complex condition involving different clinical states, subcategories and overlapping aetiologies.[1] Europe has one of the largest liver disease burdens in the world, as shown by the 2016 Global Burden of Disease (GBD) data for mortality from cirrhosis and other chronic liver diseases in Figure 2.[2] However, the epidemiological picture, risk factors, causes, potential interventions and policies against liver disease vary across the European region.

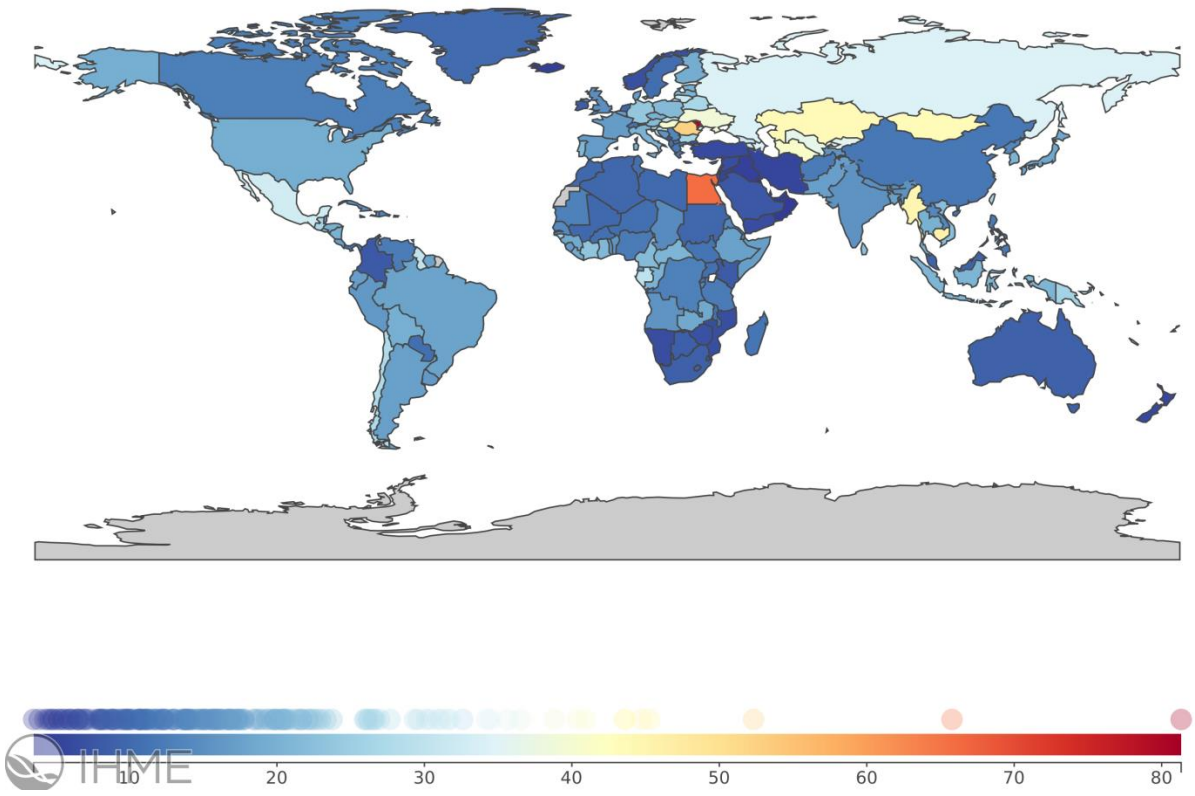


Figure 2. Mortality from cirrhosis and other chronic liver diseases for both males and females, all ages in 2016

Source: Institute for Health Metrics and Evaluation GBD 2016

The HEPAHEALTH project consists of three related reviews conducted to summarise the current epidemiological situation regarding liver disease in Europe, to examine trends in risk factors associated with liver disease and identify potential interventions and policies which could be effective in reducing the burden of liver disease. Databases summarising the data collected were collated.

This report first describes the data collected on the epidemiological burden of liver diseases in 35 European countries. The most up-to-date picture of the prevalence of and mortality from all liver diseases is presented, after which the contribution of categories of liver disease on the total burden by country is examined. The focus then shifts to on historic trends in mortality and prevalence data, by liver disease category, in order to better understand current patterns in the epidemiological data.

In the second review the current and historical patterns in the main modifiable risk factors for liver disease are summarised: alcohol consumption, obesity and diabetes. The aim was to understand the association between these risk factors and liver disease by reviewing literature and analysing collected data.

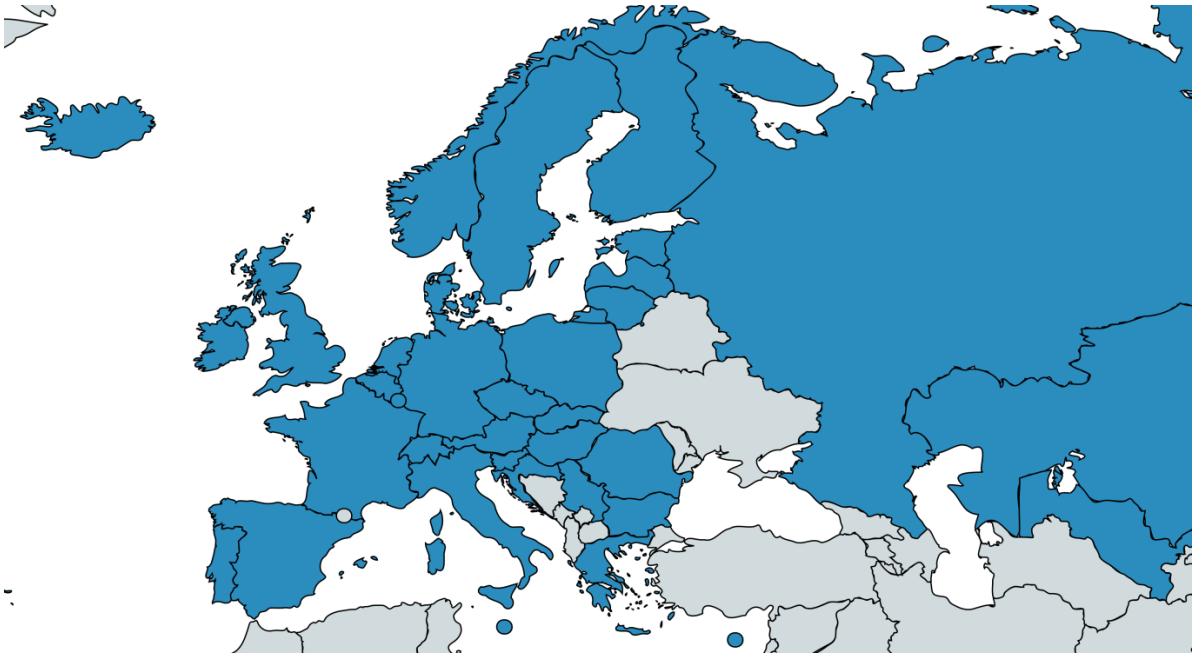
Finally, this project reports on the recent evidence behind the main public health measures and policies for reducing the burden of liver disease, through interventions aimed at the main risk factors for liver disease.

This report also contains several focus sections in which includes information on the limitations in data collection are discussed, as well as a summary of a qualitative interview study conducted on liver disease experts, in order to triangulate and supplement findings from the formal review of databases and the literature.

PART 1. THE CURRENT AND HISTORICAL BURDEN OF LIVER DISEASE IN EUROPE

Introduction

This section describes the results of the literature review which collated and reviewed data on liver disease across 35 World Health Organisation (WHO) European region countries (see Figure 3). They include the 31 European Union/European Economic Area countries plus an additional five countries that were of particular interest to the European Association for the Study of the Liver (EASL). It was beyond the timeline and scope of this project to include all 53 WHO-European region member states.



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

Figure 3. List of countries included in HEPAHEALTH project (n=35)

The full database can be downloaded from the EASL website. A summary of the data collected is provided here, but more extensive analyses can be carried out by country, sex, and age as required by the database user. Two case study examples have been prepared to illustrate the depth of the database and how it can be manipulated by age, sex and disease for individual countries.

Methods

Data on the current and historical burden of liver diseases in the 35 European countries of interest were obtained from a range of sources, involving extraction and manipulation of data from freely-available national and international databases, as well as a review of recent published and grey literature (focussing on reviews) of epidemiological data on liver disease. Finally, further potential sources of information through snowballing of contacts in the field of liver diseases were gathered.

Database data extraction

In order to maximise comparability across countries, and to use a standardised definition of liver disease, the majority of data for each epidemiological measure was obtained from online databases:

- Mortality data for liver diseases was obtained from the raw death counts by ICD-10 4-digit codes provided by the WHO European Detailed Mortality Data (DMDB)[3], recoded to represent eight liver disease categories. The WHO DMDB data was also used to estimate potential years of life lost (PYLL) for ischemic heart disease, stroke and lung cancer, to compare findings with liver disease. Additional historical data on liver disease mortality was collected for larger categories of liver disease from the WHO Health for All database.[4]
- Prevalence data for cirrhosis and liver cancer was obtained from the GBD 2016 release.[2]
- Hepatitis data was obtained from the European Centres for Disease Prevention and Control (ECDC) after a request for recent acute and chronic hepatitis B and C data disaggregated by age and sex.[5] However, use of this data was limited due to the asymptomatic nature of chronic infections, differences in screening programmes, differences in surveillance practices between countries, data quality issues and inclusion of EU/EEA countries only so data from the literature supplemented the database data. Prevalence of hepatitis B and C modelled estimates were collected from the Polaris Observatory.[6 7] Additional data for prevalence of hepatitis B and C in persons who inject drugs (PWID) was obtained from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA).[8]

Where not specified, the data presented are for both male and females combined. See supplementary material for further details on data sources, references, data manipulation and analysis.

Literature review

Reviews presenting data on the epidemiological burden of liver disease were identified and extracted using a comprehensive literature search strategy. See supplementary material for further information.

Snowballing

The sources of information identified were communicated to liver disease experts, in order to collect further information of potentially useful sources.

Data and discussion

The current burden of liver disease

Data from the GBD 2016 project[2] was used to present the age-standardised prevalence of cirrhosis and other chronic liver disease (one of the two categories of liver disease in the GBD dataset, the other being liver cancer), for males and females for all 35 countries in Figure 4. Prevalence increases from Western to Eastern European countries to some extent but is greatest in Central European countries, with more than 1100 cases per 100,000 in Austria and Romania. Countries with low prevalence of cirrhosis and other chronic liver diseases include Iceland, Norway and Sweden (with 447, 578, 597 cases per 100,000 respectively in 2016). It must be noted that GBD 2016 data comes from modelled estimates, and that the GBD modelled compensated liver disease as well as decompensated liver disease for the first time in their 2016 release, thereby increasing estimates of prevalence.

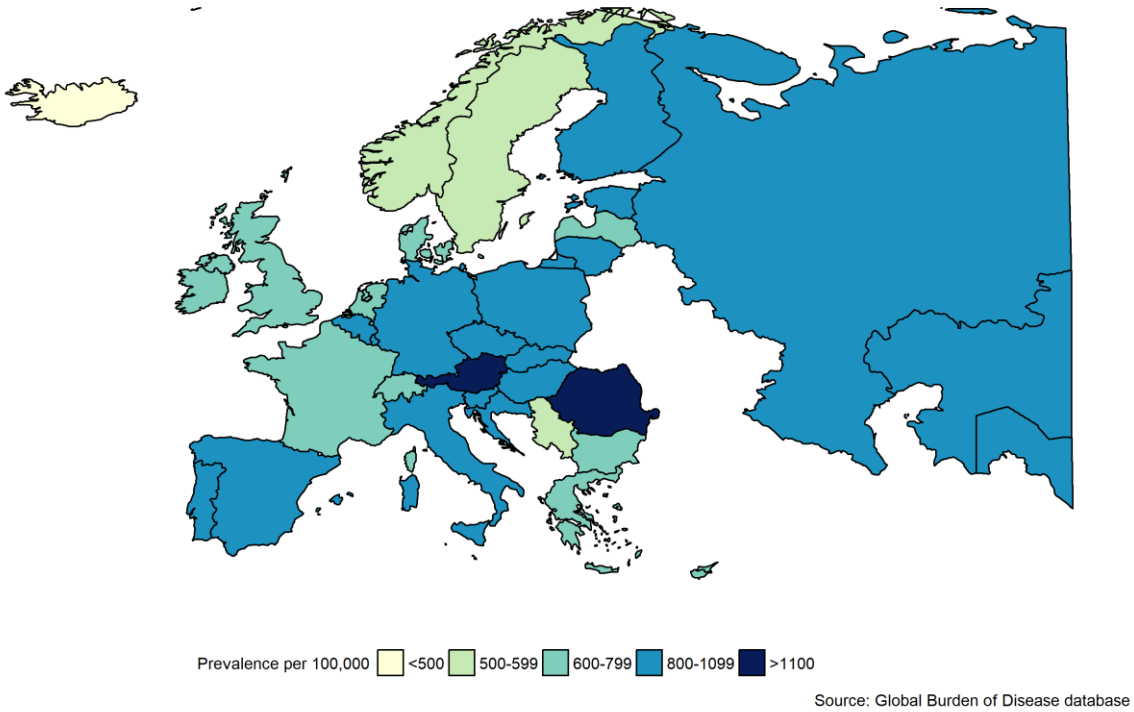


Figure 4. Age-standardised prevalence of cirrhosis and other chronic liver diseases in 2016 – modelled data
Less visible countries: Luxembourg: 1064 per 100,000 Malta: 556 per 100,000.

Figure 5 provides the breakdown of this data by four aetiology categories for cirrhosis and other chronic liver disease: alcohol use, hepatitis B infection, hepatitis C infection and other causes. The majority of the cirrhosis and other chronic liver diseases can be explained by alcohol use and hepatitis B and C infections. However, countries vary in the relative contributions of these risk factors. For instance, in most Western countries, alcohol is the most important risk factor; see Ireland, Germany and Portugal as examples. In these

countries viral hepatitis (B and C) combined contribute less than alcohol, and a smaller proportion of cirrhosis and liver disease is due to other causes. In Central European countries however, there is a shift in these proportions, with viral hepatitis and alcohol contributing approximately equally to the burden of liver disease, see Croatia and Slovenia in Figure 5. Viral hepatitis is the main determinant of disease for all ages and genders when considering countries further east. In the majority of countries hepatitis C accounts for a greater proportion of liver disease cases than hepatitis B, but in Kazakhstan and Uzbekistan hepatitis B accounts for more cases than hepatitis C.

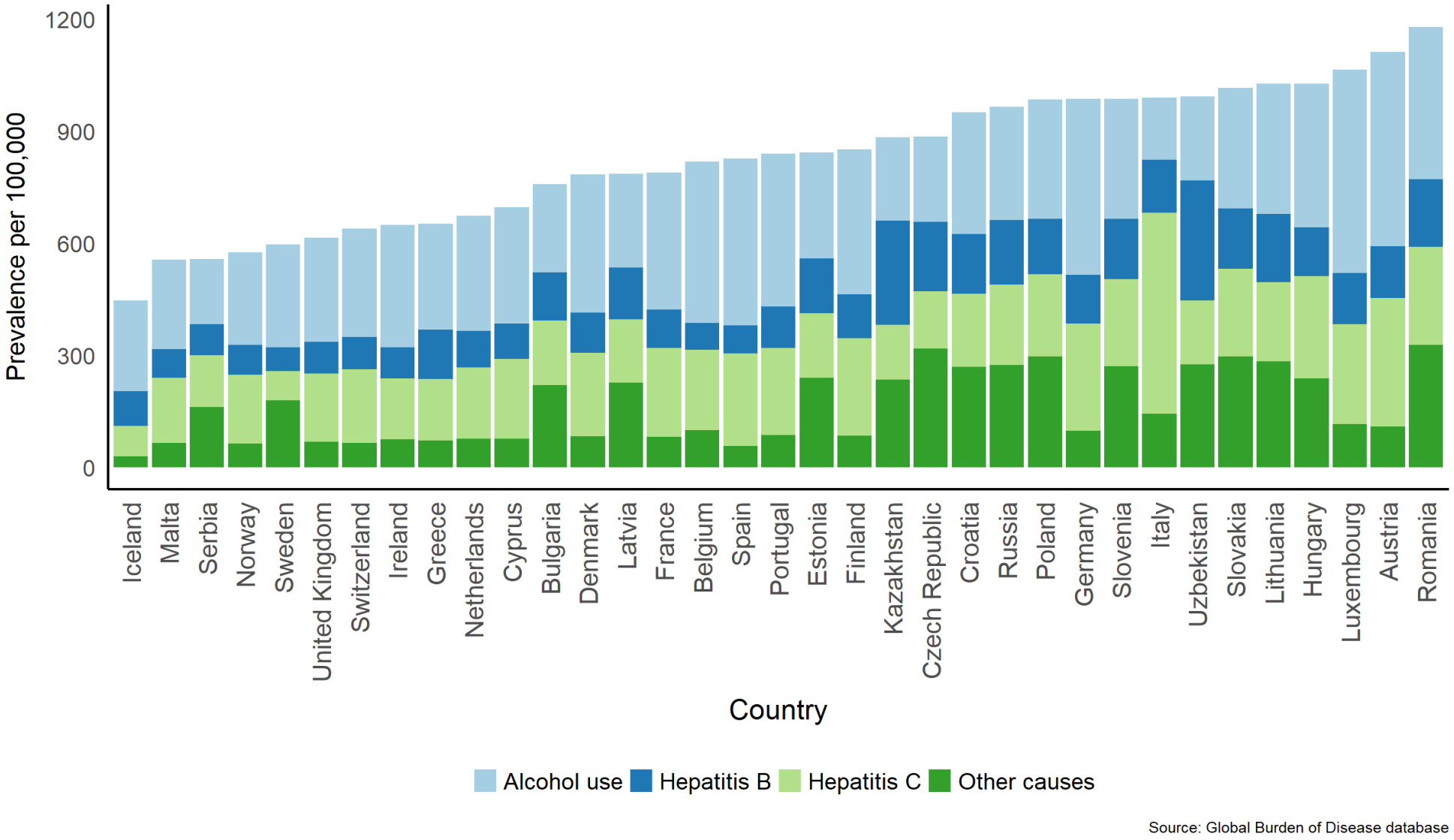


Figure 5. Age-standardised prevalence of cirrhosis and other liver diseases by aetiology in 2016 – modelled data

The GBD estimates prevalence of hepatocellular carcinoma (liver cancer), as shown in Figure 6.

Liver cancer prevalence exhibits a north-south gradient. Liver cancer rates above 12 per 100,000 were estimated for Italy, with slightly lower rates in Austria, Germany, Luxembourg and Switzerland. Prevalence of liver cancer below five per 100,000 was estimated in Poland and Hungary.

In 2015, viral hepatitis (B and C, with C being predominant) was the main aetiology behind cases of liver disease for the majority of countries, followed by alcohol use (Figure 7).

The estimated prevalence from the GBD data must be interpreted with caution: firstly, these data are modelled data, and secondly the 2016 dataset includes compensated as well as decompensated cirrhosis, which is asymptomatic but which results in large prevalence estimates, whereas the 2015 estimates just model decompensated cirrhosis (see supplementary material for further information).

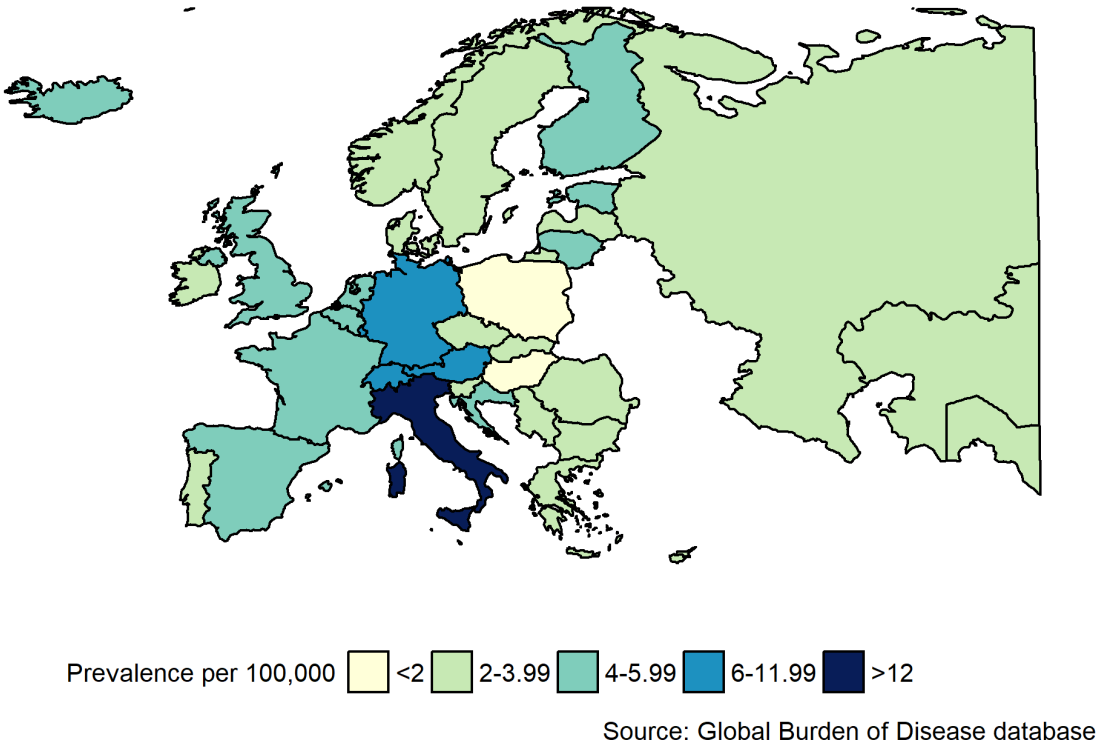


Figure 6. Age-standardised prevalence of liver cancer in 2016 – modelled data
Less visible countries: **Luxembourg**: 11.9 per 100,000 Malta: 1.6 per 100,000.

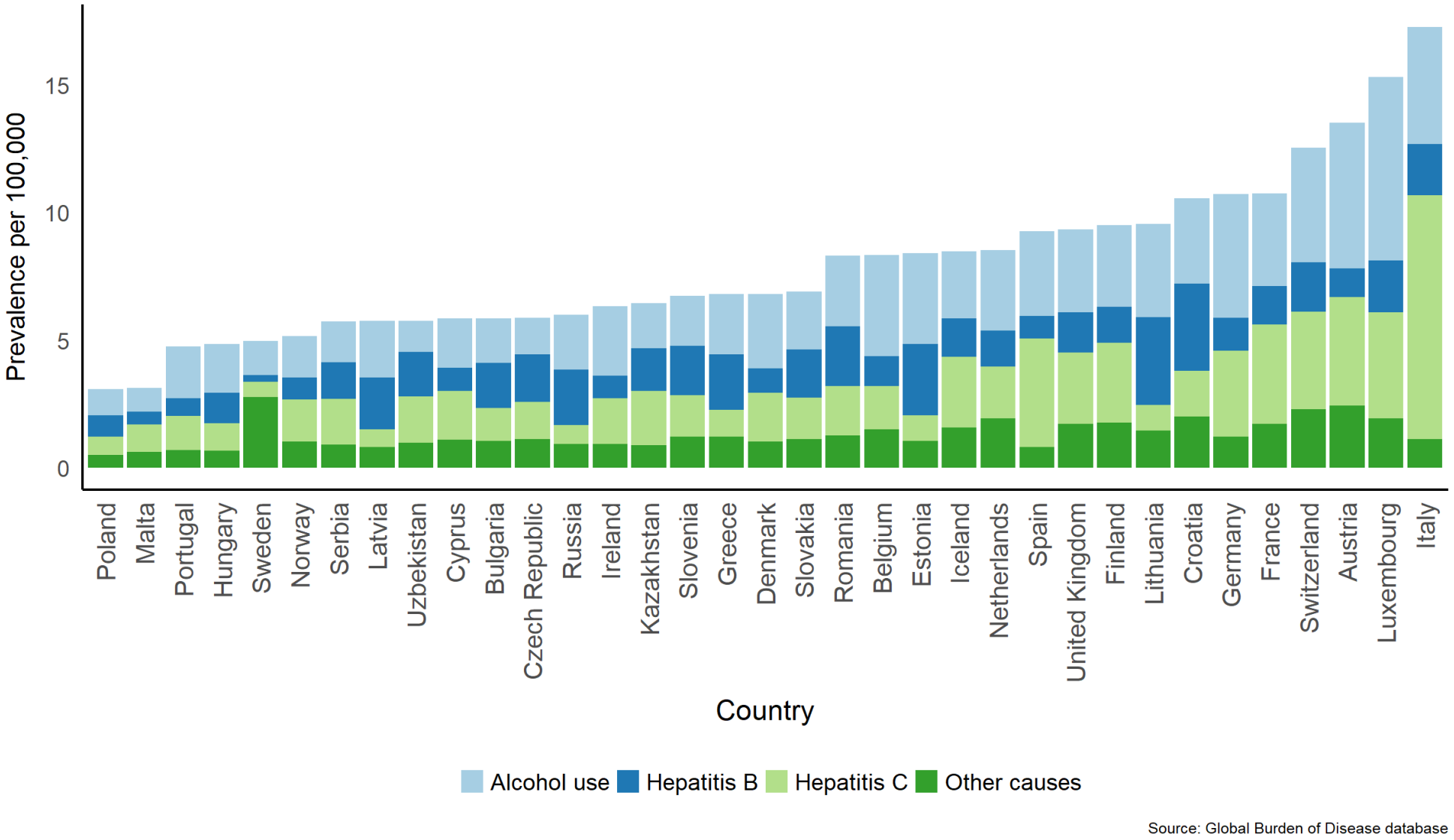


Figure 7. Age-standardised prevalence of liver cancer by aetiology in 2016 – modelled data

Using WHO raw mortality ICD-10 codes to describe the epidemiology of liver disease comes with limitations. WHO data uses primary cause of death but for patients with liver disease the direct reason for death is recorded as the primary cause, and so the deaths, often caused originally by the underlying liver disease will not be coded as liver disease. Mortality data from this source will therefore likely under-represent the mortality in people with liver disease. It is not possible to obtain data on all reported causes (underlying primary, secondary and direct) from the WHO mortality data.

Mortality rates for all liver diseases, age-standardised for comparison across countries show a similar pattern to prevalence data, for the latest year of mortality data available. The highest rates of mortality were seen in Romania (36 per 100,000) as well as Lithuania and Hungary where mortality of all liver disease was above 20 deaths per 100,000, with rates in Iceland, Norway, and the Netherlands on the lower end of the scale, below 10 deaths per 100,000 (Figure 8).

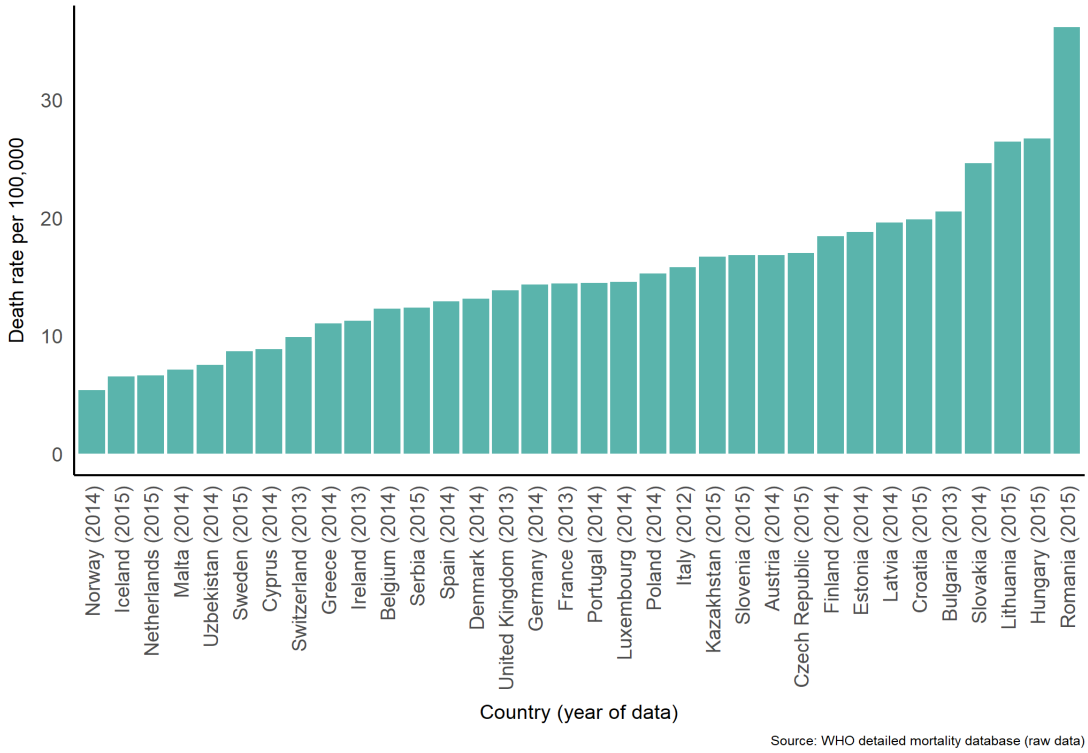


Figure 8. Age-standardised mortality for all liver diseases – in most recent year

Translating the impact of mortality into years of life lost due to deaths from all liver disease, shown in Figure 9, highlights that a large proportion of the years lost due to mortality from liver disease are working years of life lost. This indicates that on average two thirds of mortality occurs in individuals below the age of 65 years. This pattern was consistent across all countries.

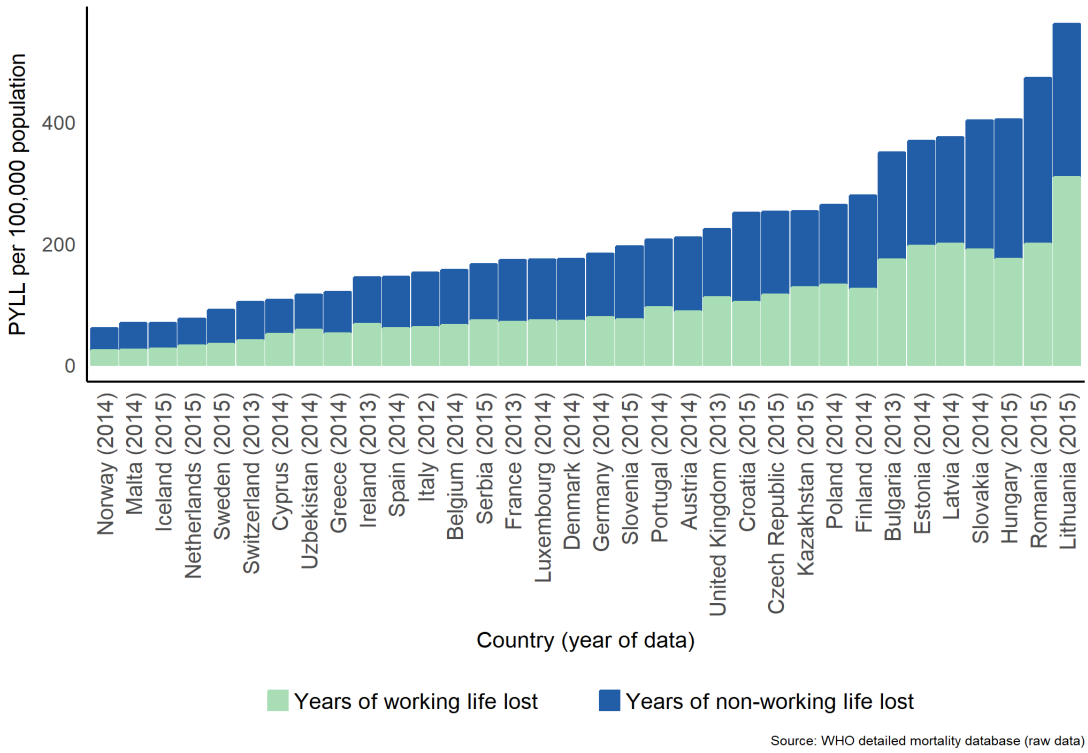


Figure 9. Age-standardised potential years of life lost (working and non-working) for all liver diseases – both genders in most recent year

The plots in Figure 10 present the potential years of life lost (both working years and non-working years) for the largest chronic disease causes of death in Europe (i.e. ischemic heart disease, stroke and lung cancer).

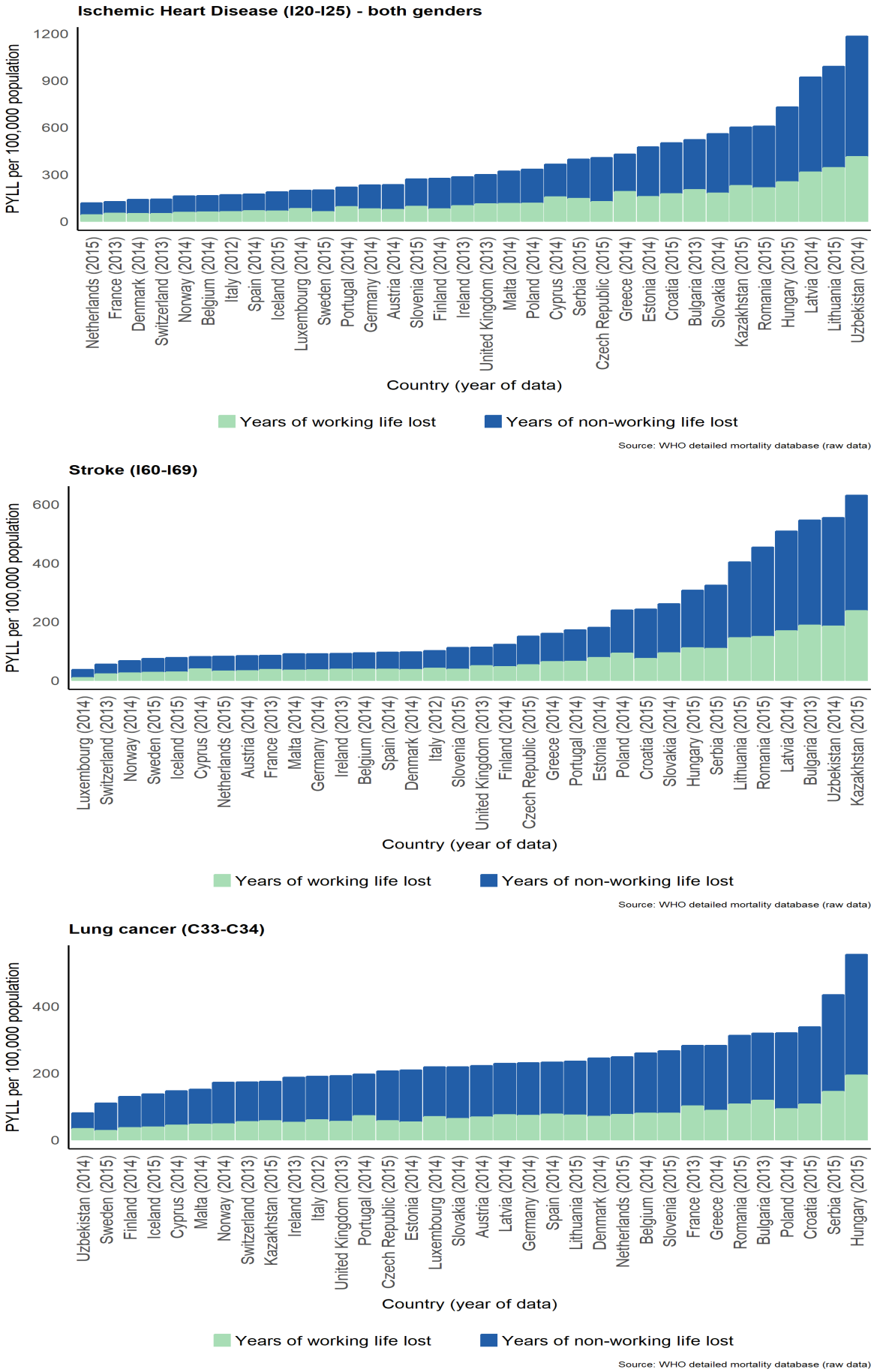


Figure 10. Age-standardised potential years of life lost (working and non-working) for ischemic heart disease, stroke and lung cancer – both genders in most recent year

When considering the breakdown of mortality from all liver disease by broad category of liver disease for the most recent years available, (Figure 11) some patterns emerged:

Alcohol. Alcohol is a large contributor to the mortality rate of many countries, although interestingly it has the lowest contribution in countries with the highest proportion of liver disease mortality from unknown causes. This may be due to differences in ICD-10 coding, as it is not clear how reliable coding is in some situations, where medical professionals aim to avoid stigmatisation for cirrhosis patients.[9] Liver disease deaths related to alcohol represents the largest proportion of deaths in Slovakia, Slovenia and Poland as well as the Czech Republic and Germany in Eastern and Central Europe, and in the majority of Northern countries with high rates, including Denmark, Estonia, Finland and the United Kingdom. Liver cancer is the greatest contributor to total mortality in the remaining Northern European countries, which show lower overall mortality rates.

Liver Cancer. Cancer, compared to other types of liver disease represents a large proportion of deaths for the majority of countries, including all Western and some Southern countries, see France, Italy, Luxemburg, Portugal, Spain and Switzerland.

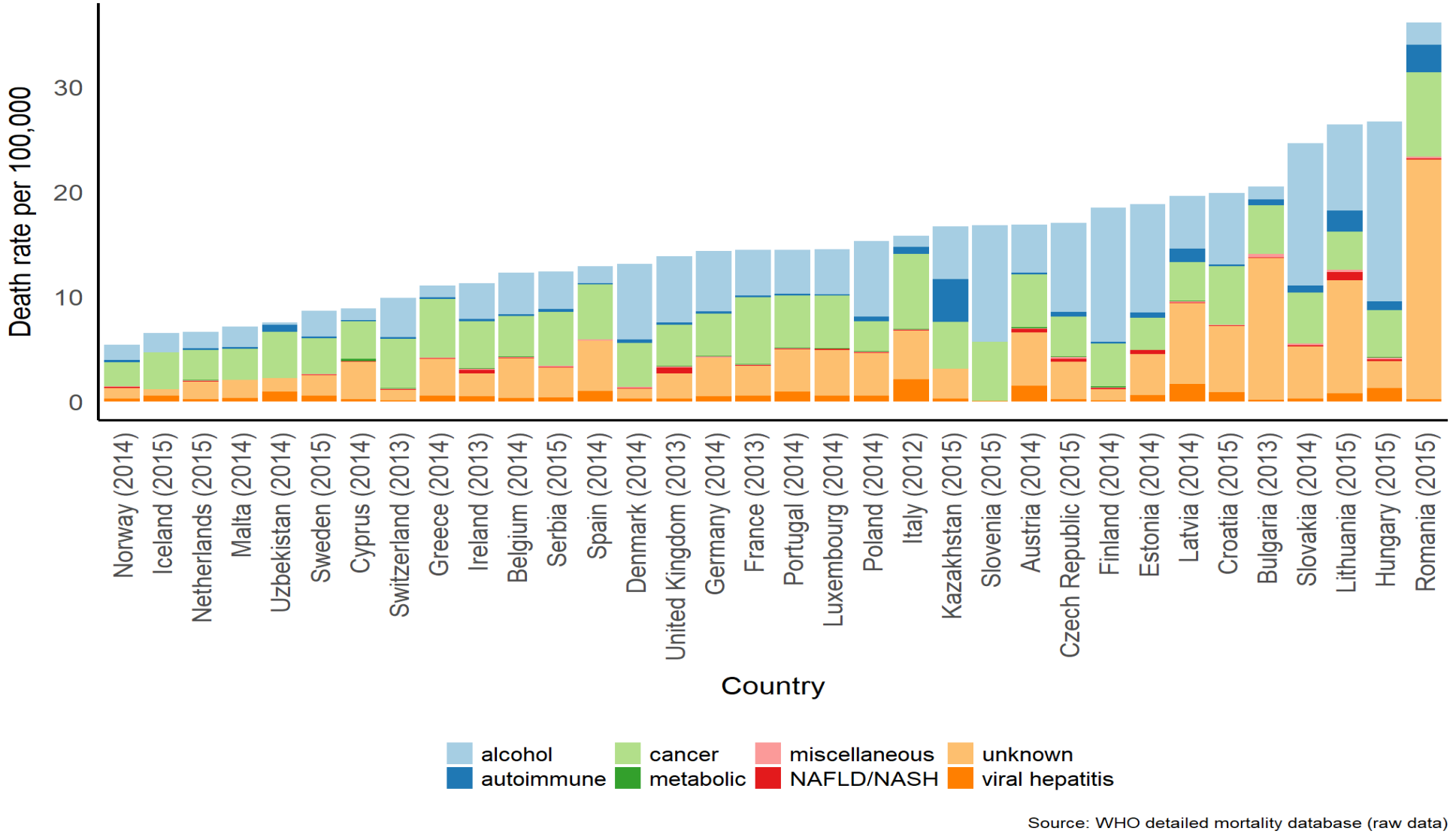
Viral hepatitis. Viral hepatitis is a visible contributor to total liver disease, in particular in Southern countries (Italy and Spain) but also Austria, Hungary and Latvia. However, for the majority of other countries, other aetiologies and diseases are more predominant. This should not be taken as an indication of the total burden of viral hepatitis in liver disease. These mortality data represent the primary cause of death coded on death registration. While viral hepatitis is a significant determinant of liver disease, it may not be recorded as the primary cause of death: for instance hepatitis infection leads to hepatocellular carcinoma, and this might instead be the cause of death recorded.

Non-alcoholic fatty liver disease (NAFLD)/ non-alcoholic steatohepatitis (NASH). NAFLD and NASH coded as the cause of death are most common in Ireland, Hungary, Luxembourg and the United Kingdom. These are countries which are currently leading in terms of the obesity epidemic (this correlation will be discussed in part 2 of this report). It is not a large proportion of the primary cause of death in the majority of European Countries – while it may be a larger contributor to the burden of liver disease, other nonspecific causes of death are given to these cases.

Autoimmune liver disease. Autoimmune liver disease appears much higher in Eastern countries (Hungary, Kazakhstan Lithuania, Latvia, Romania and Uzbekistan) for example. For other countries, autoimmune liver disease is a small, but still noticeable fraction of all deaths, especially when compared with other less common types of liver disease, including portal hypertension and metabolic liver disease.

Metabolic and miscellaneous liver disease. These types of liver disease represent a very small proportion of the overall burden of liver disease in almost all European countries.

These patterns need to be interpreted cautiously, in light of the fact that this is based on only one year of mortality reporting. Smaller countries, with lower total cases of liver disease, may experience more year on year variation in the absolute proportions of types of liver disease, compared to countries with larger absolute numbers of cases. In addition, as discussed above, countries appear to vary in the proportion of deaths allocated to a cause, or unknown. While Romania has the highest total mortality rate, it also has the greatest proportion of cases allocated to codes for which the aetiology or type of disease is ‘unknown. This makes comparisons between countries difficult.



Source: WHO detailed mortality database (raw data)

Figure 11. Age standardised mortality from all liver disease by aetiology in the most recent year available for each country

Unknown code category: K74.6 Other and unspecified cirrhosis of liver and, K72.0 Acute and subacute hepatic failure and K72.9 Hepatic failure, unspecified, were the most common ICD-10 codes represented. K74.6 represented above 50% of all deaths in 29 countries, while K72 codes represented over 50% in three countries. In Denmark K74.6 and K72 codes together represented 66% of all unknown codes; in Slovenia I81 Portal hypertension represented 100% of all deaths. Miscellaneous code category: K75.0 Abscess of liver representing over 50% of all miscellaneous deaths in 14 countries, with K74.4 Secondary biliary cirrhosis, K75.1 Phlebitis of portal vein, and K76.1 Chronic passive congestion of liver, K763 Infarction of liver, K764 K76.4 Peliosis hepatitis and K768 Other specified diseases of liver representing over 15% of all cases in all countries.

The current picture of cirrhosis, other liver diseases and liver cancer prevalence shows heterogeneity across Europe, and different patterns in aetiology. These are due to variations across populations in terms of the main risk factors for liver disease, but also to differences in how liver diseases are defined, recorded and reported in different countries. The difference in the proportion of cases coded as unknown across European countries (Romania compared to Denmark, for example) shows a deficit in coding, but also that this can be resolved if solutions are developed and applied properly.

An exploration into the trends over time can help explain the current epidemiological burden of liver disease. Looking first at trends over time in mortality and prevalence of disease, followed by reporting in Part 2 of the review focussing on trends in specific liver disease risk factors will allow a greater understanding and interpretation of the European situation concerning liver disease.

Historic trends in liver disease mortality

The current epidemiology of liver disease in European countries can in part be explained by historical trends. Furthermore, different trajectories across countries may highlight differences in demographics but also changes in risk factors and policies, from which it would be possible to learn lessons and develop strategies for the future. Mortality data from the DMDB, using ICD-10 codes to standardise definitions of types of liver diseases is available from the 1990s, but less granular data from the WHO Health for All database provides historical data, albeit for much broader categories. This data was used to apply a long-term perspective, plotting standardised mortality from liver diseases, from 1970 to 2015.

The 34 HEPAHEALTH countries which provided cirrhosis and chronic liver diseases mortality data (Russia not included) can be categorised into four broad groups: countries which have increasing or decreasing rates of mortality, and those remaining high but stable and remaining low but stable.

Figure 12 presents the population-weighted average mortality over time, while Figure 13 presents the country-level time trends for each of the four groups.

Mortality has decreased from initial rates between 20 and 42 per 100,000 in countries from Western and Southern Europe (Austria, Croatia, France, Germany, Greece, Italy, Luxembourg, Portugal, Slovenia, Spain and Switzerland).

A separate subset of countries, including Bulgaria, Estonia, Finland, Hungary, Kazakhstan, Latvia, Lithuania, Romania and the United Kingdom were categorised as having large increasing trends in liver disease between 1970 and 2015. These predominantly Northern and Western countries varied in their absolute rates per 100,000 with a population-weighted average trend increasing gradually, from the end of the 1980s.

Slovakia and Uzbekistan were two Eastern countries that had rates which were stable over the 45 year period, but which were at a relatively high level (above 20 deaths per 100,000), compared to a range of other countries with stable mortality, but in many cases much lower than 20 or even 10 deaths per 100,000 (Belgium, Cyprus, Czech Republic, Denmark, Iceland, Ireland, Malta, Netherlands, Norway, Poland, Serbia and Sweden). Although rates are age and total population standardised, it is interesting to note that these low but stable countries are relatively small European countries (with the exception perhaps of Poland).

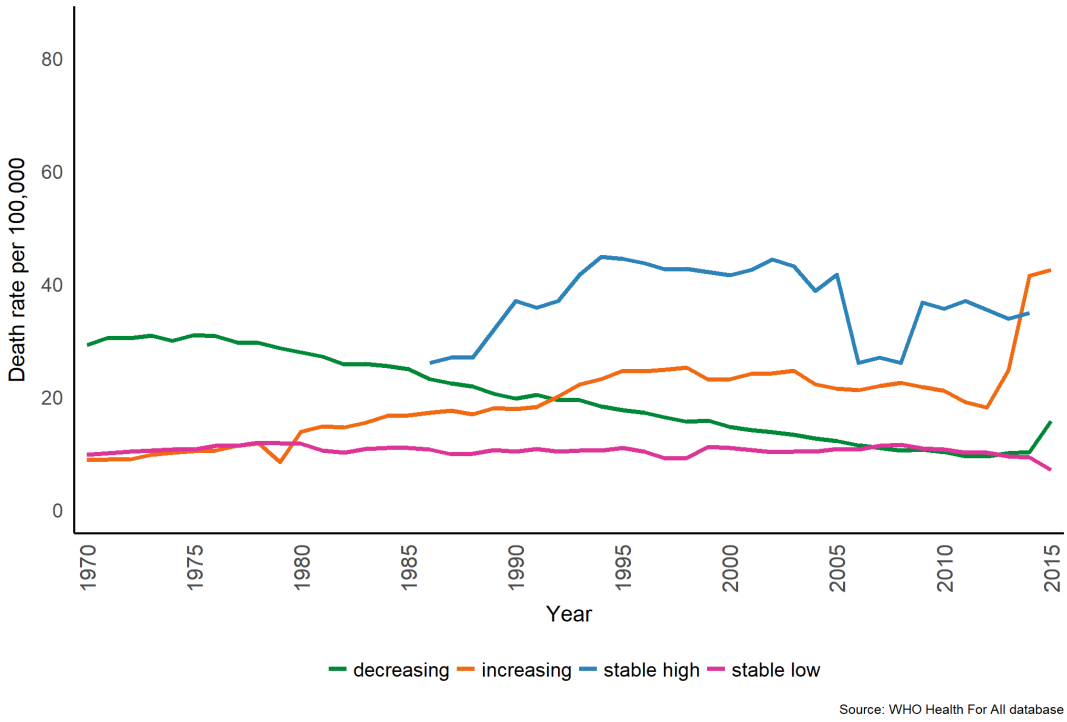


Figure 12. Population-weighted average mortality rate for cirrhosis and other chronic liver diseases over time for countries in four trend groups (decreasing, increasing, stable-high and stable-low)

The up-turn between the years 2012-2014 for some of the average trends are caused by only a limited number of countries providing data up to 2014/2015. For this reason, the very recent trends should not be considered, as they may be skewed by data from only one or two countries in each group.

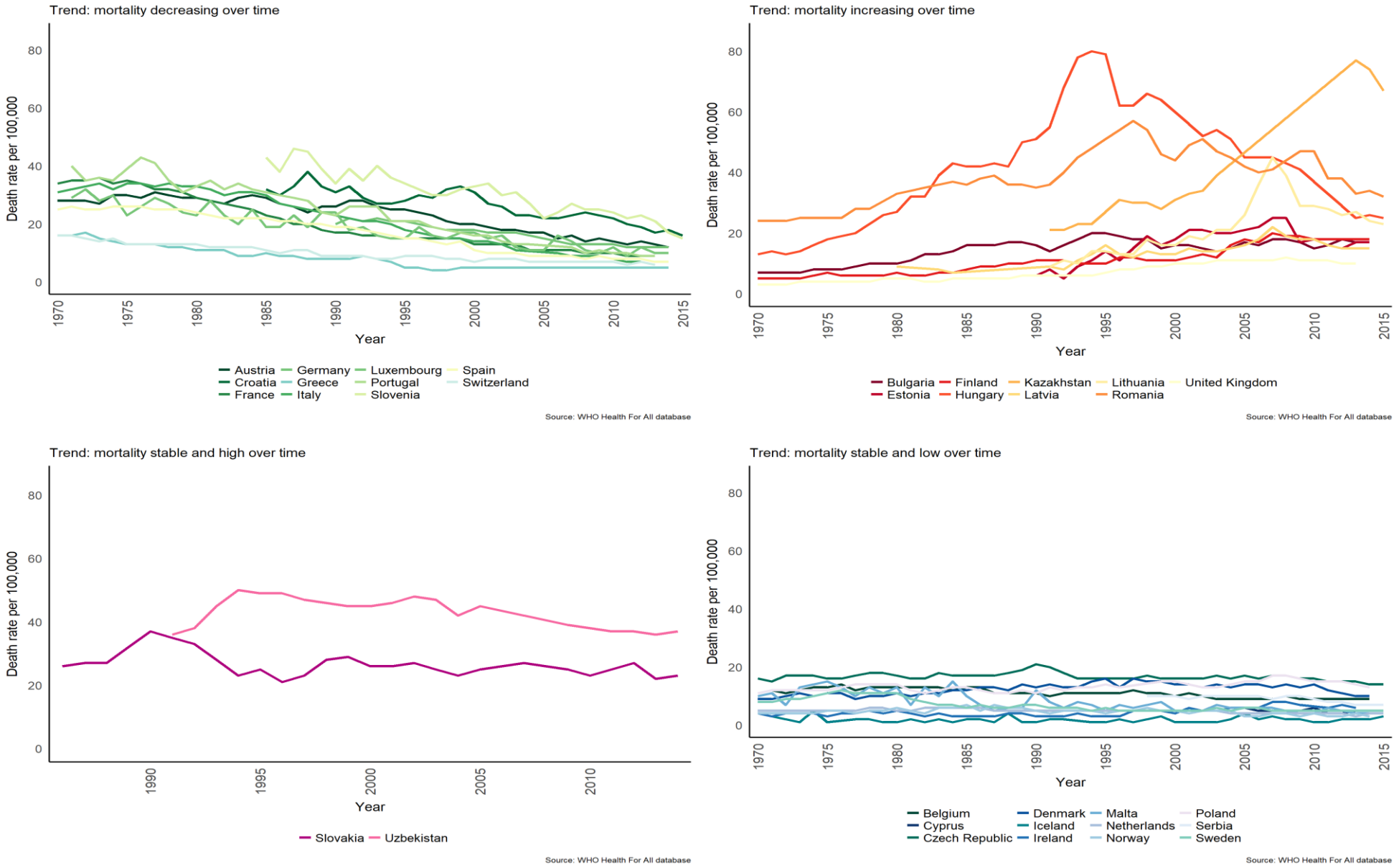


Figure 13. Mortality rate for cirrhosis and other chronic liver diseases over time for countries in four trend groups (decreasing, increasing, stable-high and stable-low)

In Figure 14, the population weighted average mortality for liver cancer over time is plotted for countries grouped according to whether the liver cancer mortality rate from 1980 to 2014 was increasing, decreasing, stable at a high rate or stable low.

Liver cancer mortality rates have increased for a majority of countries (Austria, Czech Republic, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Portugal, Romania and the United Kingdom), while only a few countries have experienced small decreases in mortality (Bulgaria, Hungary, Kazakhstan, Poland and Spain). Spain's mortuary rates dropped significantly between 1980 and 1985, after which rates increases slightly. Remaining countries had relatively stable rates, either above five deaths per 100,000 from liver cancer, in countries such as Croatia, Russia, Serbia, Slovakia, Slovenia, Switzerland and Uzbekistan, or at a slightly lower mortality rate, for countries including Belgium, Cyprus, Denmark, Estonia, Iceland, Latvia, Lithuania, Malta, Netherlands, Norway and Sweden). It should be noted that data was not available for all years since 1980 in the mortality database from the WHO Health for All explorer, so that trends may not be representative of the country's true experience (see Figure 15).

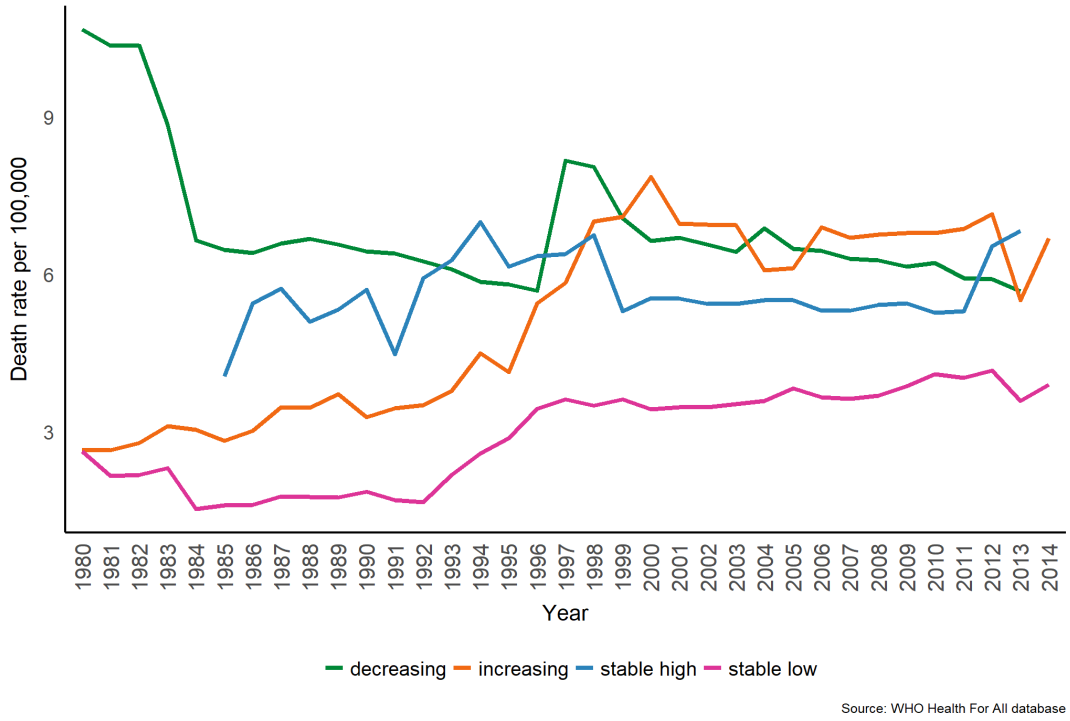


Figure 14. Population-weighted average mortality rate for liver cancer over time for countries in four trend groups (decreasing, increasing, stable-high and stable-low)

The up-turn between the years 2012-2014 for some of the average trends are caused by only a limited number of countries providing data up to 2014/2015. For this reason, the very recent trends should not be considered, as they may be skewed by data from only one or two countries in each group.

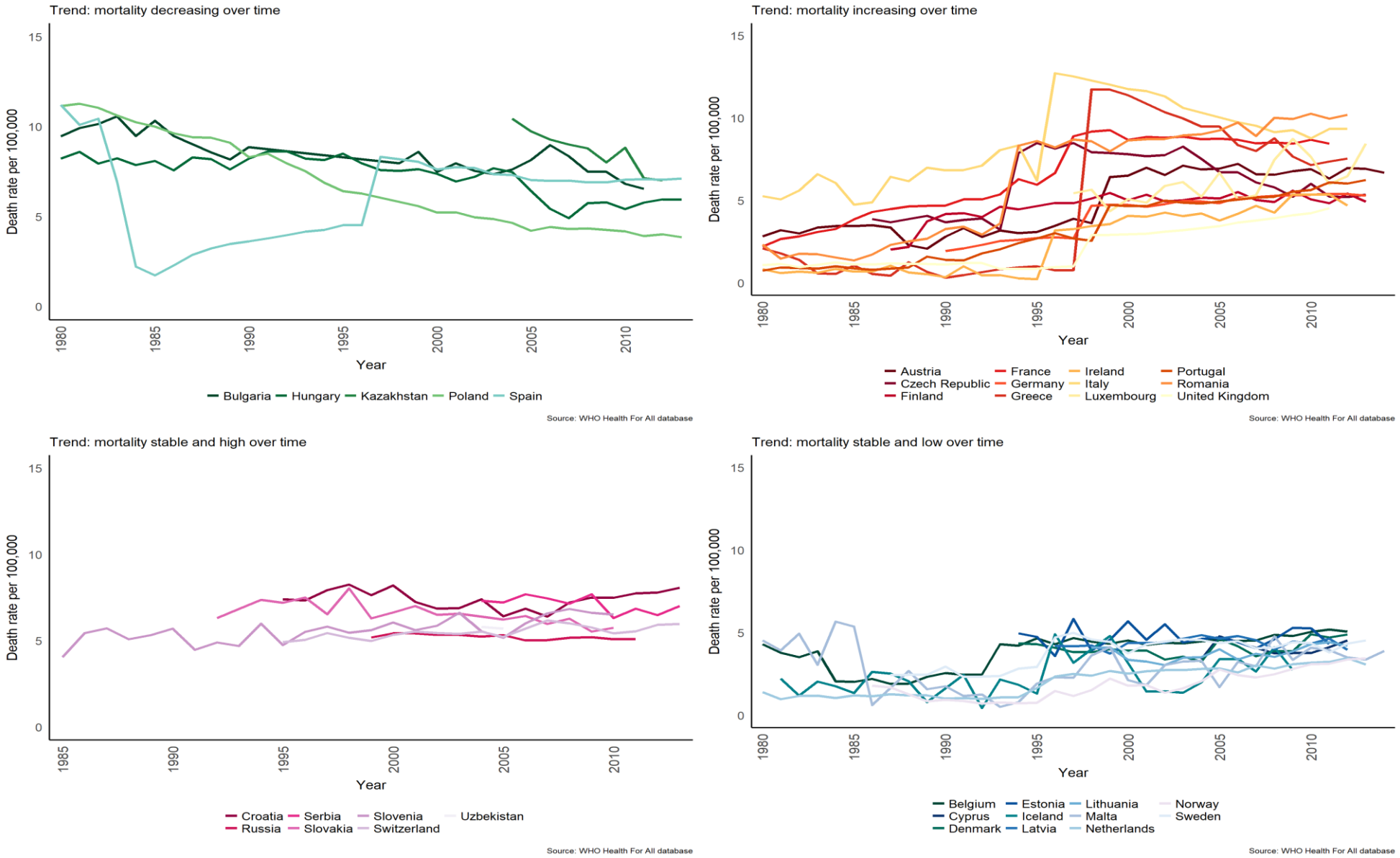


Figure 15. Mortality rate for liver cancer over time for countries in four trend groups (decreasing, increasing, stable-high and stable-low)

Breakdowns of mortality rates from all liver diseases, age-standardised and for both males and females, plotted by four sub regions for Europe (North, East, South and West) are shown in Figure 16. These were plotted using the ICD-10 codes form the European Detailed Mortality Database, and so data is only available from the time that the ICD-10 was implemented, unlike long-term trends in broad disease categories obtained from the Health for All database in the Figures above (Figure 12 and Figure 13).

Initial observation of these graphs show that mortality trends in countries in Eastern Europe needed to be plotted on a scale twice that of Southern and Western countries, while Northern countries required a similar scale to accommodate data from Lithuania. In these Northern countries, however, the overall trend was a stable rate of mortality for the majority of countries (Denmark, Iceland, Ireland, Norway, Sweden and the United Kingdom), while Estonia and Finland have shown an increase in mortality. Latvia and Lithuania have also increased since 1994, but trends appear to now be stabilising.

In Eastern countries, trends were also stable over the last 20 years for the Czech Republic, Poland and Uzbekistan. Large decreases in mortality were recorded for Kazakhstan and Romania while Bulgaria and Slovenia had stable rates around 15 to 20 deaths per 100,000, increasing in recent years.

In Southern countries, mortality rates ranged between five and 35 deaths per 100,000, with a variation in time trends; Malta and Cyprus were stable with overall lower mortality rates, Croatia had higher mortality rates which were decreasing over time, Italy, Portugal and Spain had slight decreases in mortality over time, Slovenia saw recent increases, and Serbia had a past decrease, leading to stable rates in recent years.

Countries in Western Europe showed overall stable trends over time, with slight deceases in mortality rates since the late 1990s for Austria, France, Germany and Luxembourg.

While this pattern is interesting in itself, a more accurate picture of trends in liver disease mortality over time can be obtained when considering different types of liver disease. The plots in Figure 17 to Figure 19 present the same mortality trends by country and region, but for alcoholic liver disease, non-alcoholic liver disease and viral hepatitis separately.

From the overall picture of these regional breakdowns by the three diseases, it is clear that alcoholic liver disease is the largest burden and highest priority in the North of Europe, while viral hepatitis is the highest priority in the East and South.

Trends in alcoholic liver disease can largely be broken down into three groups: in Northern and Eastern Europe, mortality either increased since the mid-90s, as in Estonia, Finland, Latvia and Lithuania, or remained constant (see Figure 17), while alcoholic liver disease mortality in Western and Southern European countries either remained constant or showed significant decreases over the last two decades. This pattern was replicated for NALFD/NASH (see Figure 18).

There was an increasing trend in mortality rates from NAFLD/NASH in Northern countries, while rates in Western, Southern and Eastern countries were generally lower and stable. However, caution must be applied when interpreting data on mortality from non-alcoholic liver disease before the 2000s, as it is unlikely that these codes represent current understanding on NAFLD or NASH. In contrast, mortality rates from viral hepatitis were higher in Southern, Eastern and Western European countries.

Mortality from liver cancer appears to be stable or increasing in the majority of European countries. In a few countries (especially in Eastern Europe, liver cancer rates are decreasing), see Figure 20.

Intrahepatic cholangiocarcinoma is a rare cancer which, over the last several decades, has shown a steadily increasing incidence and mortality rates. Figure 78 in supplementary material demonstrates that mortality from intrahepatic cholangiocarcinoma is increasing in all regions over time. The number of intrahepatic cholangiocarcinoma deaths represents just under a third of all liver cancer deaths recorded in this time period. Rates are similar across Europe with approximately two deaths per 100,000 populations. Eastern Europe shows the lowest intrahepatic cholangiocarcinoma deaths per 100,000, although this could be explained by data collection and coding of ICD-10 codes. Ireland and the United Kingdom have relatively high mortality rates compared to the other Northern European countries, and these rates are rising sharply. Finland had historically high mortality rates, but unlike most countries their mortality rate has decreased with time. Spain and Croatia show a consistent rise in intrahepatic cholangiocarcinoma deaths per 100,000 over the last 20 years, while Malta and Cyprus have had more fluctuating trends. All of Western Europe has seen a steady increase in mortality, except for Luxembourg which has an inconsistent pattern.

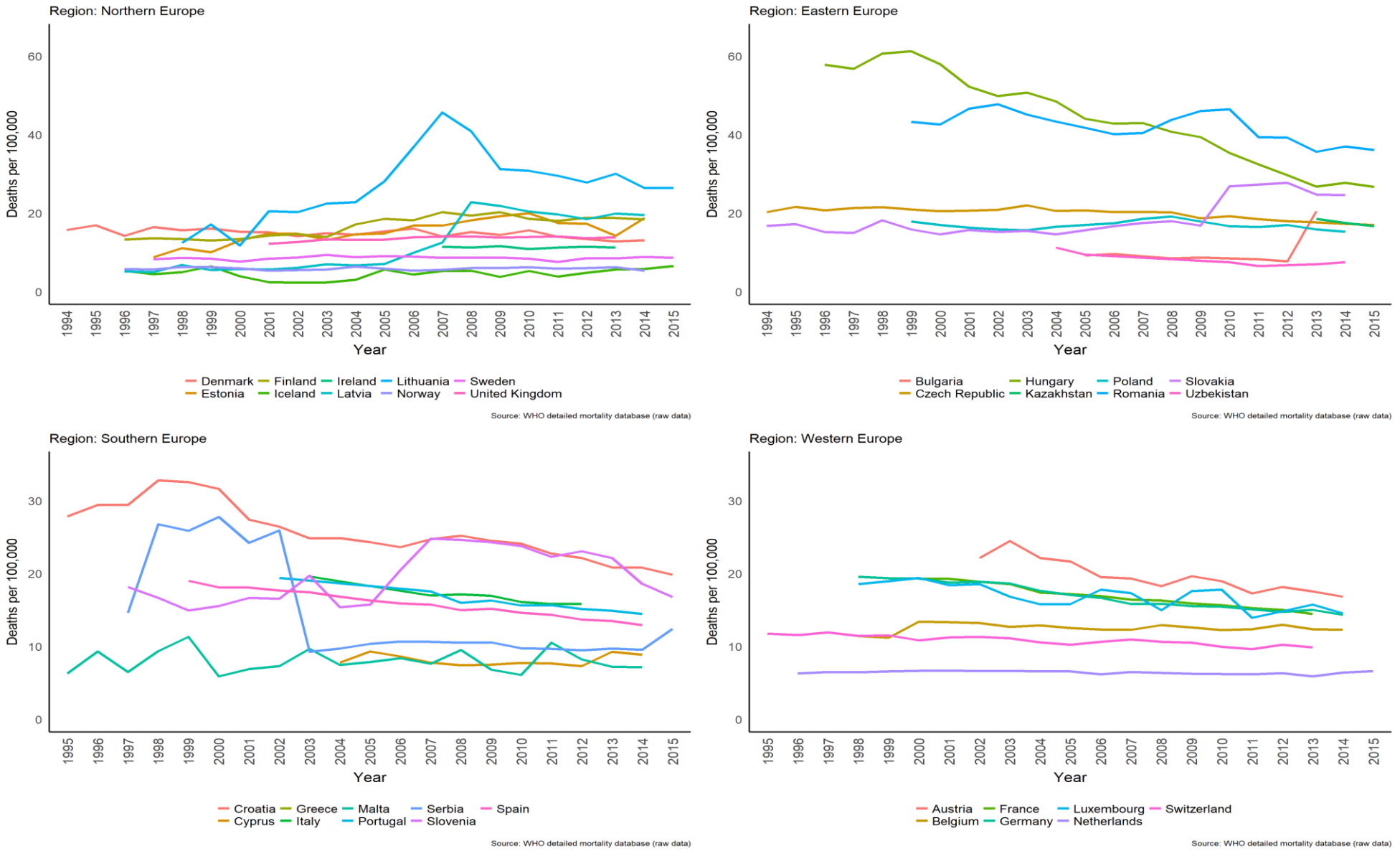


Figure 16. Time trends in age-standardised mortality from all liver diseases - both genders by region

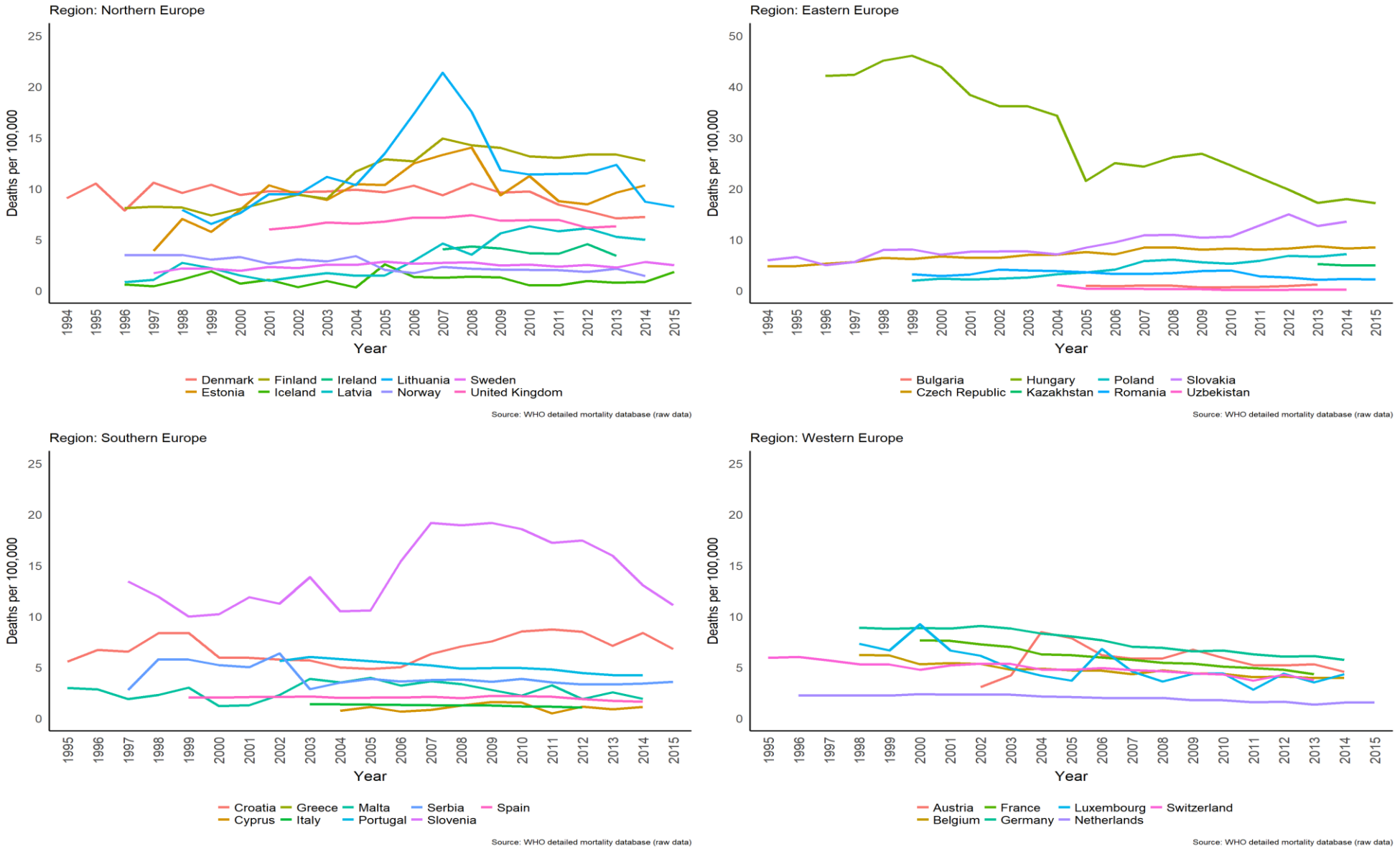


Figure 17. Time trends in age-standardised mortality from alcoholic liver diseases - both genders by region

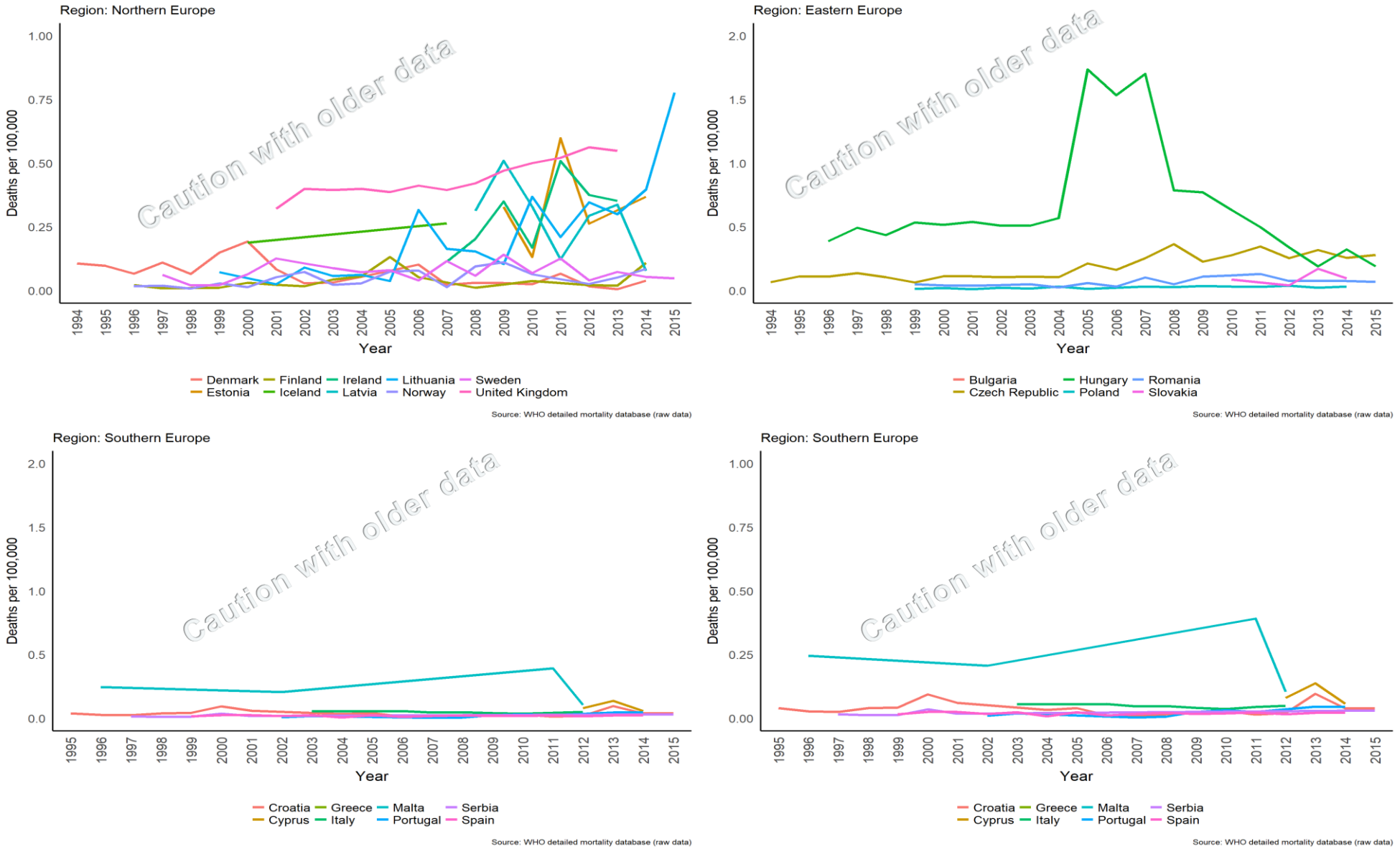


Figure 18. Time trends in age-standardised mortality from NAFLD/NASH - both genders by region

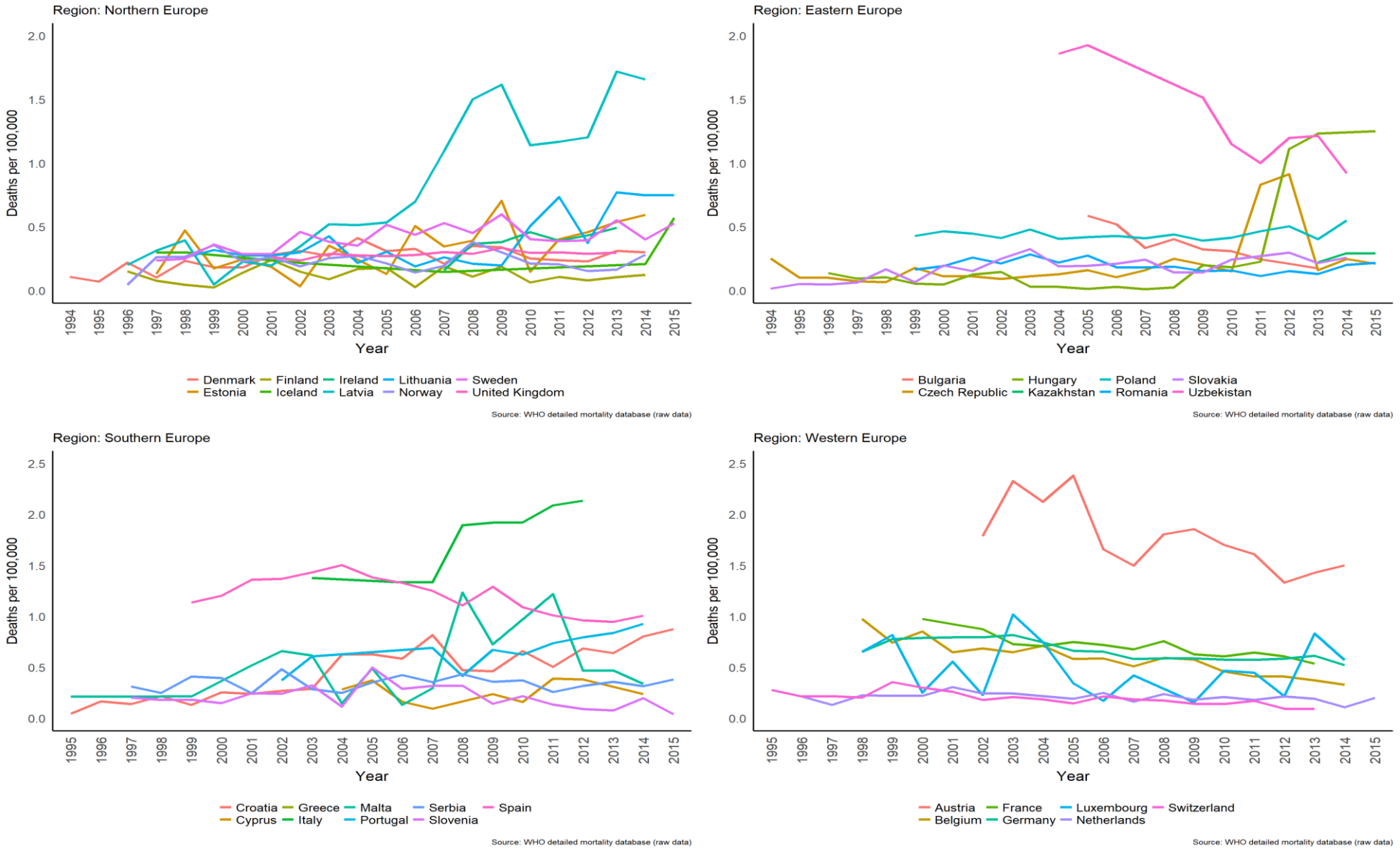


Figure 19. Time trends in age-standardised mortality from viral hepatitis - both genders by region

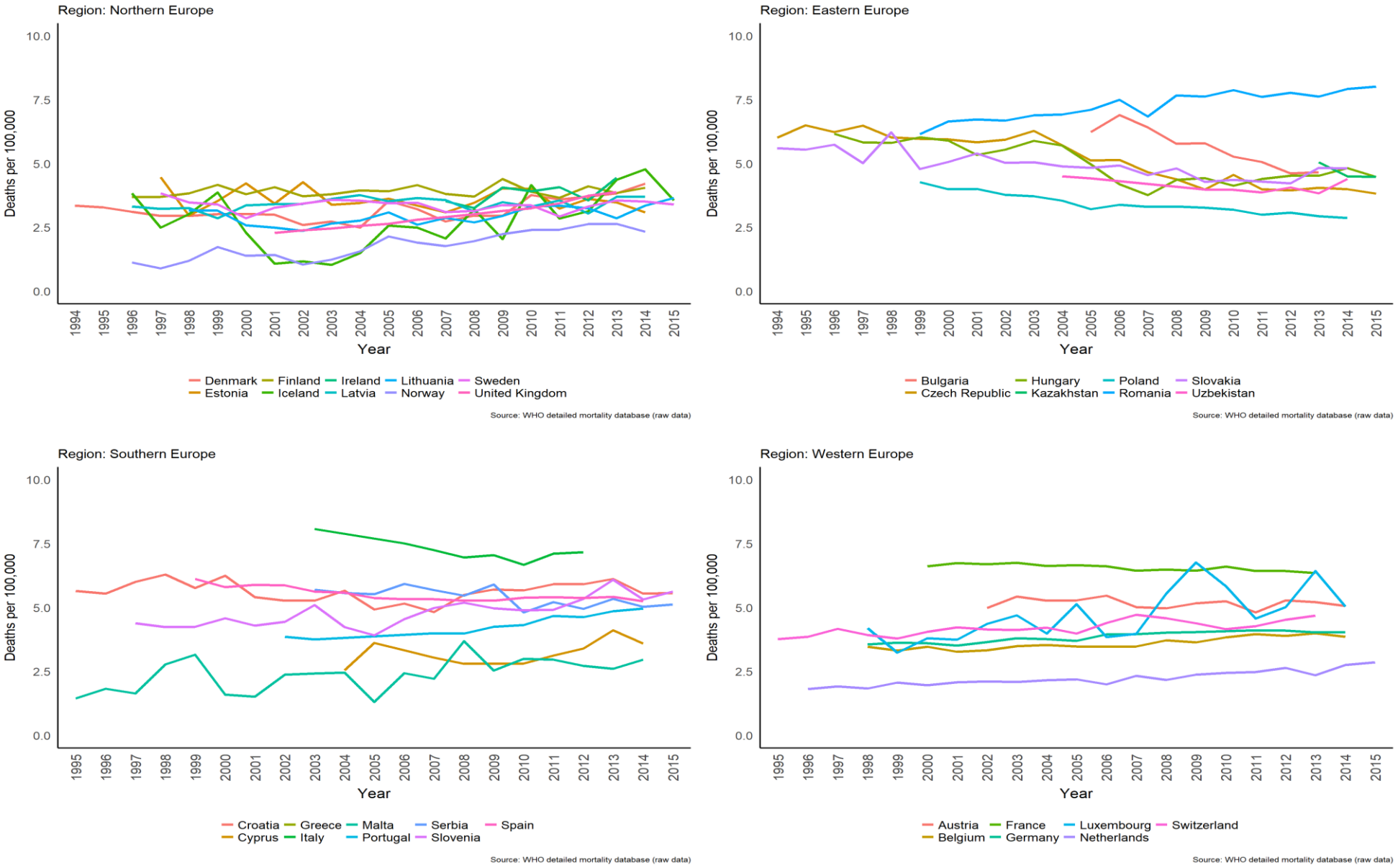


Figure 20. Time trends in age-standardised mortality from liver cancer - both genders by region

Historic trends in liver disease prevalence

Since 1990, all countries have seen increases in cirrhosis and other chronic liver disease, except for Hungary which shows a decrease and Croatia and Slovenia where rates have remained constant since 1990.

However the rate of change has not been the same for all countries, as can be seen in the time-trends for all countries by region (see Figure 21). Sharper increases in prevalence between 1990 and 2016 can be seen in countries in Northern Europe, while countries in Southern Europe have had slower increases and in some cases little change over the last two decades.

A breakdown of the aetiology of liver diseases for one country representing the four European sub regions is shown in Figure 22.

The increase in prevalence in Northern and Eastern European countries such as the United Kingdom and Russia appears to be largely due to alcohol use, with an equivalent increase in chronic liver disease due to other causes in Russia.

Time trends for Western and Southern countries, such as Cyprus, in particular show that while cirrhosis and other liver diseases due to alcohol are significant contributors to the total burden, the increase in total prevalence can largely be attributed to increases in cases due to hepatitis B and C infection.

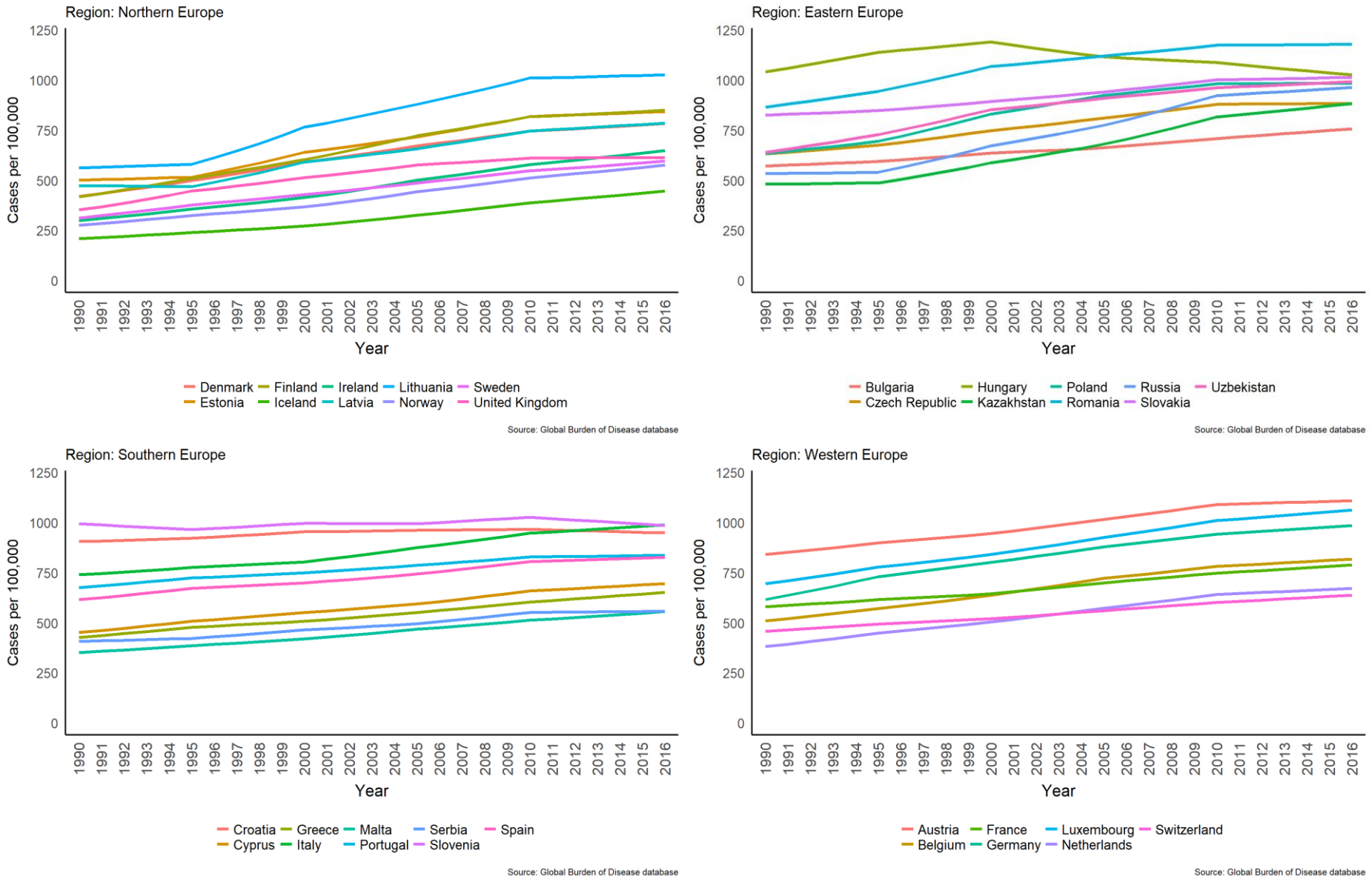


Figure 21. Time trends in age-standardised prevalence of cirrhosis and other chronic liver diseases - both genders – modelled data

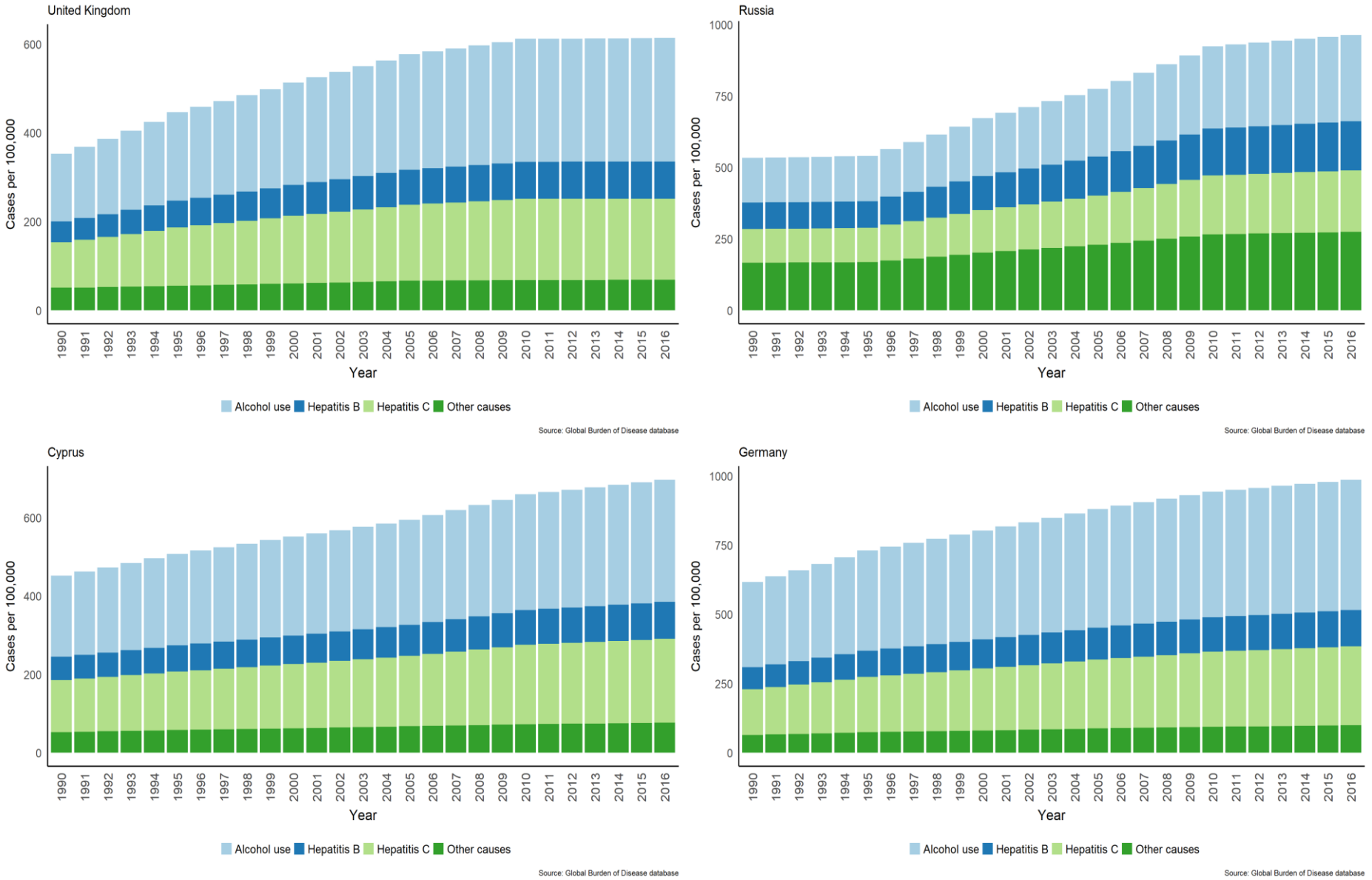


Figure 22. Time trends in aetiology of cirrhosis and other chronic liver diseases prevalence for one example country from each region – modelled data

Liver cancer prevalence has increased since 1990 in the majority of European countries, with the exception of Hungary and Kazakhstan where rates have decreased, and Denmark, Poland and Uzbekistan, where rates have remained largely stable over time, as shown in Figure 23. Figure 24 shows the causes of liver cancer prevalence over time in four countries representing the four UN sub regions. Alcohol and especially hepatitis B and C are important contributors to the increase in total liver disease cases in the United Kingdom, representing the trend in Northern European countries and in Western Europe, represented by Germany. High rates of liver cancer in countries of Eastern Europe such as Russia were maintained and increased due to increases in cases attributed to alcohol and hepatitis B, while increases in Southern countries such as Cyprus were largely due to increases in liver disease due to hepatitis B and C.

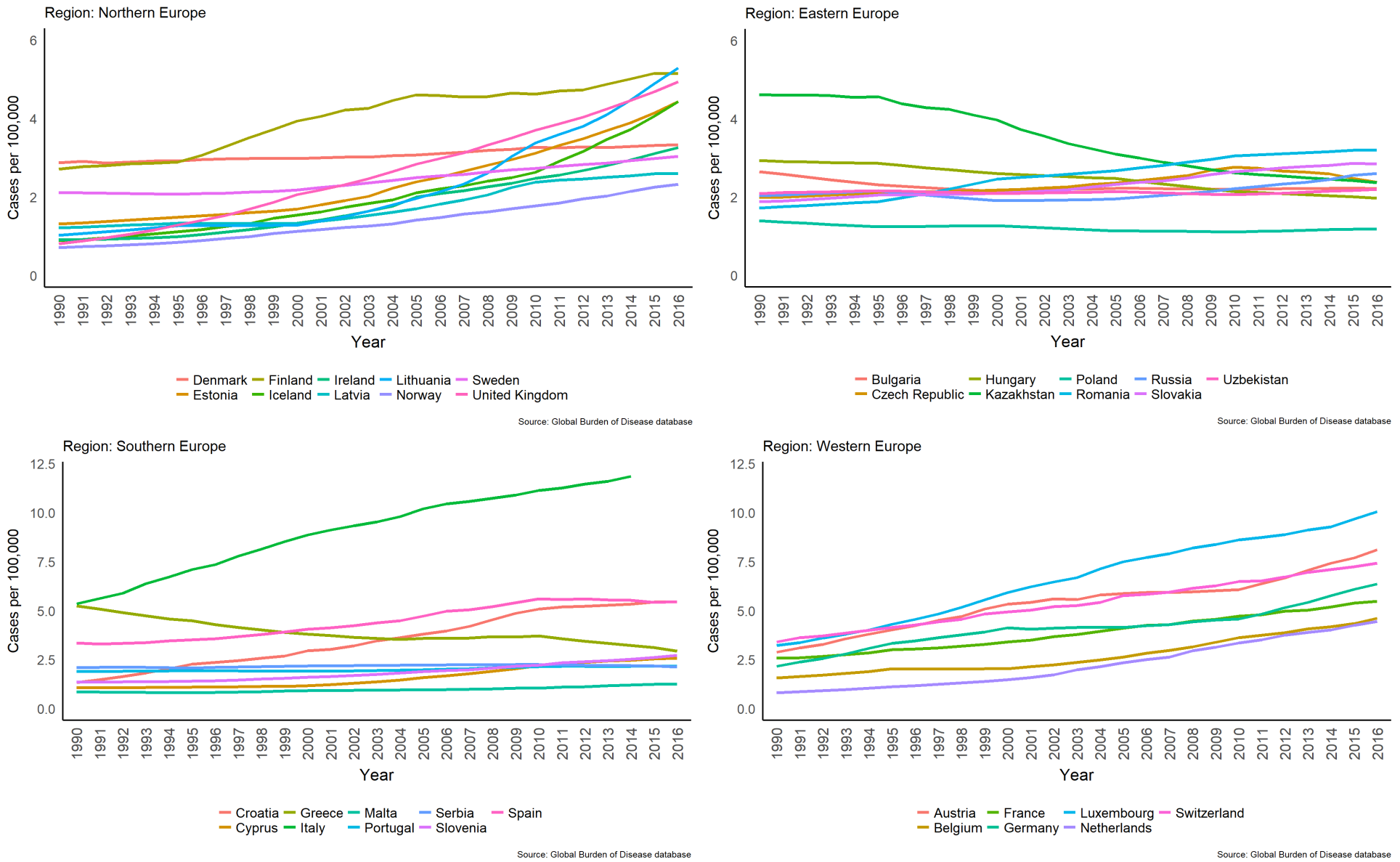


Figure 23. Time trends in age-standardised prevalence of liver cancer - both genders – modelled data

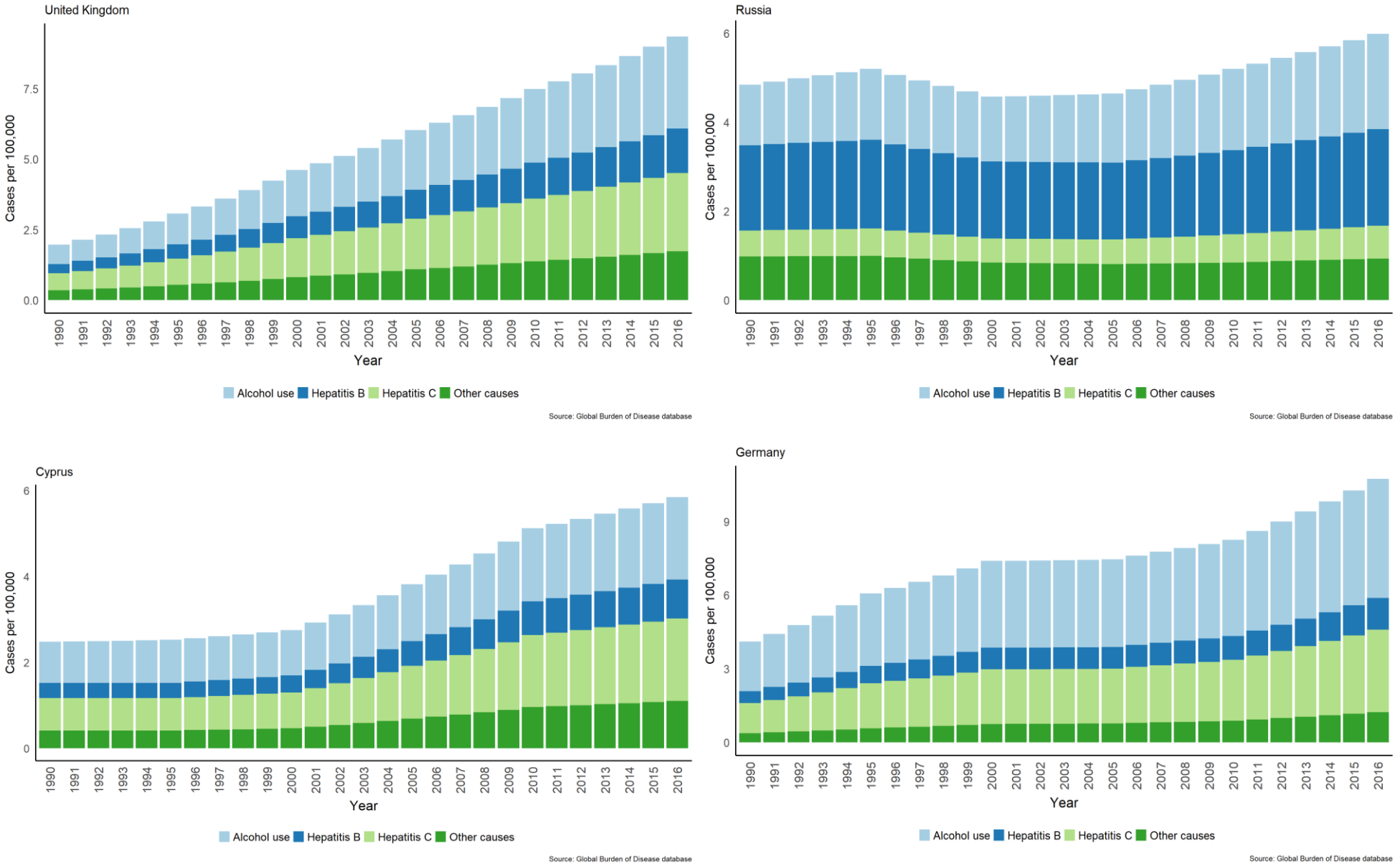


Figure 24. Time trends in aetiology of liver cancer prevalence for one example country from each region – modelled data

The burden of hepatitis B and C infection

This review focusses on epidemiological data for hepatitis B and C, as they are the main hepatitis virus to lead to chronic liver disease. Hepatitis D is not included in this report, as it is transmitted through contact with people already infected with Hepatitis B.

Hepatitis B

Hepatitis B virus is transmitted by exposure of mucosal membranes or non-intact skin to infected blood or other specific body fluids (saliva, semen and vaginal fluid). Transmission can occur from mother to child and from person to person. Hepatitis B transmission can occur even in the absence of visible blood, e.g. by sharing toothbrushes or razors, contact with exudates from dermatologic lesions, contact with saliva through bites or other breaks in the skin, needle stick injuries or re-use of needles and syringes, sharing of chewing gum or food items, or contact with hepatitis B-contaminated surfaces. Among adolescents and adults major routes of infection are sexual transmission by contact with semen or vaginal fluid, and percutaneous transmission through the use of contaminated needles such as in injecting drug use.[10] As an asymptomatic infection, the gold standard for assessing chronic hepatitis B prevalence in a population is to conduct a seroprevalence survey on a randomised representative sample.

Systematic reviews of such studies have been performed in recent years, although all have been limited by the availability of high-quality, recent, representative nationwide prevalence estimates, especially in younger age groups: a WHO-funded systematic review (2016)[11] of national-level prevalence estimates of chronic hepatitis B infection – via seroprevalence surveys for hepatitis B surface antigen (HBsAg) in the general population dating from 1965 to 2013 found European estimates ranging from 0.01% in the United Kingdom and Norway to 6.99% in Uzbekistan (see Figure 25). The ECDC also conducted a review of Hepatitis B seroprevalence data in general populations in EU/EEA countries between 2000 and 2015 and found 0.9% prevalence of HBsAg positives in the general population, with a total of 4.7 million chronic Hepatitis B cases. These two reviews do not consistently provide the same estimates of Hepatitis B prevalence: for instance Schweitzer *et al.* (2015) estimate France to have <0.5% prevalence using HBsAg while ECDC's review 0.6-1% prevalence. In contrast Schweitzer *et al.* (2015) provide estimates of HBsAg prevalence for countries, which do not appear ECDC's estimates (e.g. Bulgaria (1.1-2%), or Sweden (0.6-1%)), see Figure 25. An update review extending Schweitzer *et al.*'s (2015) review to data up to 2017 is in preparation but the database of country-level prevalence estimates was not available.[12]

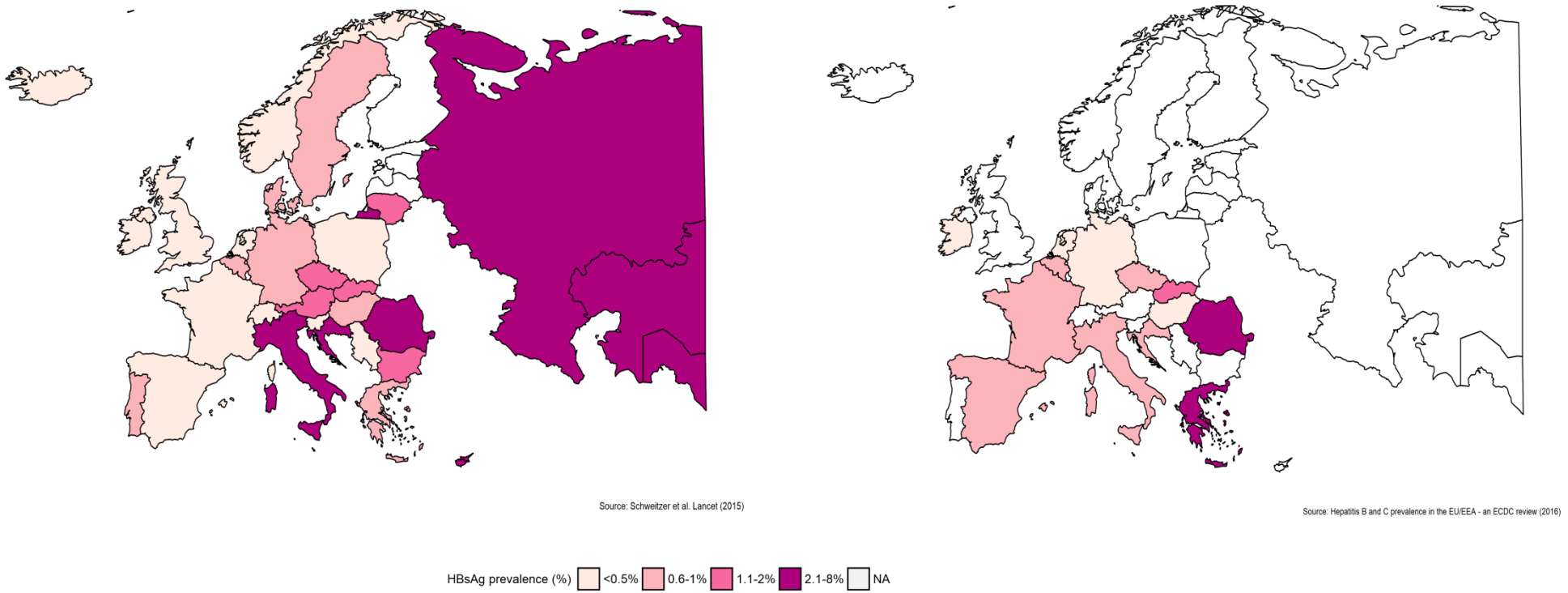


Figure 25. Chronic hepatitis B prevalence estimates from 1965 to 2013 in Lancet review and 2005 to 2015 in ECDC review

Less visible countries: Luxembourg: no data, Malta: no data

Both studies showed regional variation with higher rates in countries in Eastern and Southern Europe compared to Northern and Western countries. These figures are likely to be an underestimation as a result of inclusion of prevalence estimates among blood donors as proxy for the general population in the absence of other evidence. For this reason, data from the latest systematic reviews was triangulated and compared to the modelled estimates of HBsAg prevalence from the Polaris Observatory[6] (see Figure 79 in supplementary Material).

HBsAg prevalence was fairly stable / slightly decreasing in Northern Europe between 2007 and 2017, and all countries had less than 1.5% prevalence. Countries in Southern and Western Europe showed decreasing trends and had less than 2% and 1% HBsAg prevalence, respectively. Eastern Europe had stable / decreasing trends and had less than 5% HBsAg prevalence in all countries other than Uzbekistan which had just below 10% prevalence in 2007 and just under 8% prevalence in 2017.

A time-trend analysis of the WHO seroprevalence study revealed a decrease in overall Hepatitis B prevalence globally, but in Europe, separate trends were detected[13]:

Countries such as Poland and Russia have seen rising HBsAg prevalence over time, which could be in part due to strong political and social changes since 1963, which have increased access to injectable drugs. In countries with historically low endemicity, such as France, Germany and Spain, little reduction over time has been seen, while other countries with low Hepatitis B endemicity have seen large annual reductions (>5% annual change). These include the United Kingdom, but also countries such as Greece and Slovenia with trends that mirror those seen in high income Eastern Mediterranean states. A fourth group of countries are those with medium to low endemicity, who have seen a medium relative decrease of around 5% per year.

These results from seroprevalence in Europe indicate variation between countries, with an overall increase in cases reported and a decrease (albeit heterogeneous, and for several countries, an increase) in the prevalence of hepatitis B virus. This can be in part 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 since implementation of hepatitis B vaccination in some countries in the late 1990s. Other factors that could explain variations over time and between countries 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, see Part 2: Trends in risk factors for liver disease in Europe.

Hepatitis C

In the ECDC's recent review of hepatitis C virus using estimates of prevalence from antibody to hepatitis C virus or anti-Hepatitis C (see Figure 26) was considered representative for the general population were available for 13 countries, with the reported prevalence ranging from 0.1% (Belgium, Ireland and the Netherlands) to 5.9% (Italy)[14]. A global estimation of prevalence of Hepatitis C by Petruzziello *et al.* (2016) estimates a prevalence of 1.8% in Europe, accounting for over 13 million estimated cases.[15]

The modelled data from Polaris Observatory (see supplementary material), shows that between 2007 and 2017 the prevalence of viremic hepatitis C infections were estimated to be largely stable in Northern Europe, but increasing in Latvia. All countries had less than 2.5% prevalence. Prevalence tended to stable in Southern Europe except in Italy and Spain where it decreased, and all countries had less than 2% prevalence. In Western Europe, Switzerland and Luxembourg had decreasing trends in viremic hepatitis C prevalence, while the remaining countries were stable. All Western European countries had less than 1.5% prevalence. Eastern European countries had less than 3.5% viremic hepatitis C prevalence, and were generally stable, apart from Romania and Kazakhstan where prevalence decreased over the period, and Russia where it increased.

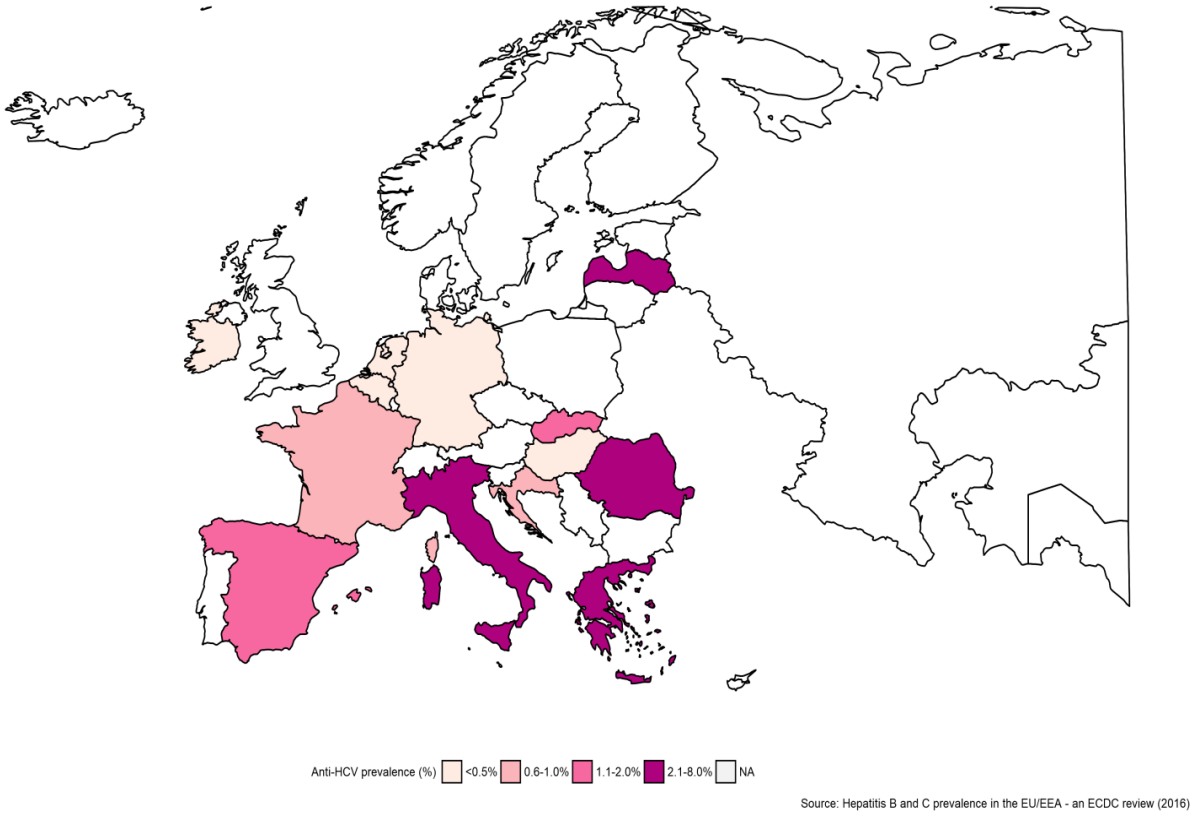


Figure 26. Chronic hepatitis C prevalence estimates from ECDC 2005-2015
Less visible countries: **Luxembourg**: no data, Malta: no data

Interpretation of both hepatitis B and C is limited, and trends are likely a reflection of testing and screening practices. The mix of acute and chronic cases, the lack of availability of good quality, timely, nationally-representative, general-population level data are limitations to the use of hepatitis B and C new cases and prevalence data. Age at infection is an important determinant of the risk of developing chronic hepatitis B, with probabilities decreasing with age, but a 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. As a largely sub-clinical disease, information on cases of hepatitis should be supplemented with seroprevalence survey data, but these are often undertaken in selected population groups, exclude high risk populations such as PWID, or migrants. More robust prevalence estimates are needed to gain further insights into the size of the populations with chronic hepatitis B or

C infections, both with regard to the general population in countries and in specific risk groups.

Liver transplantations

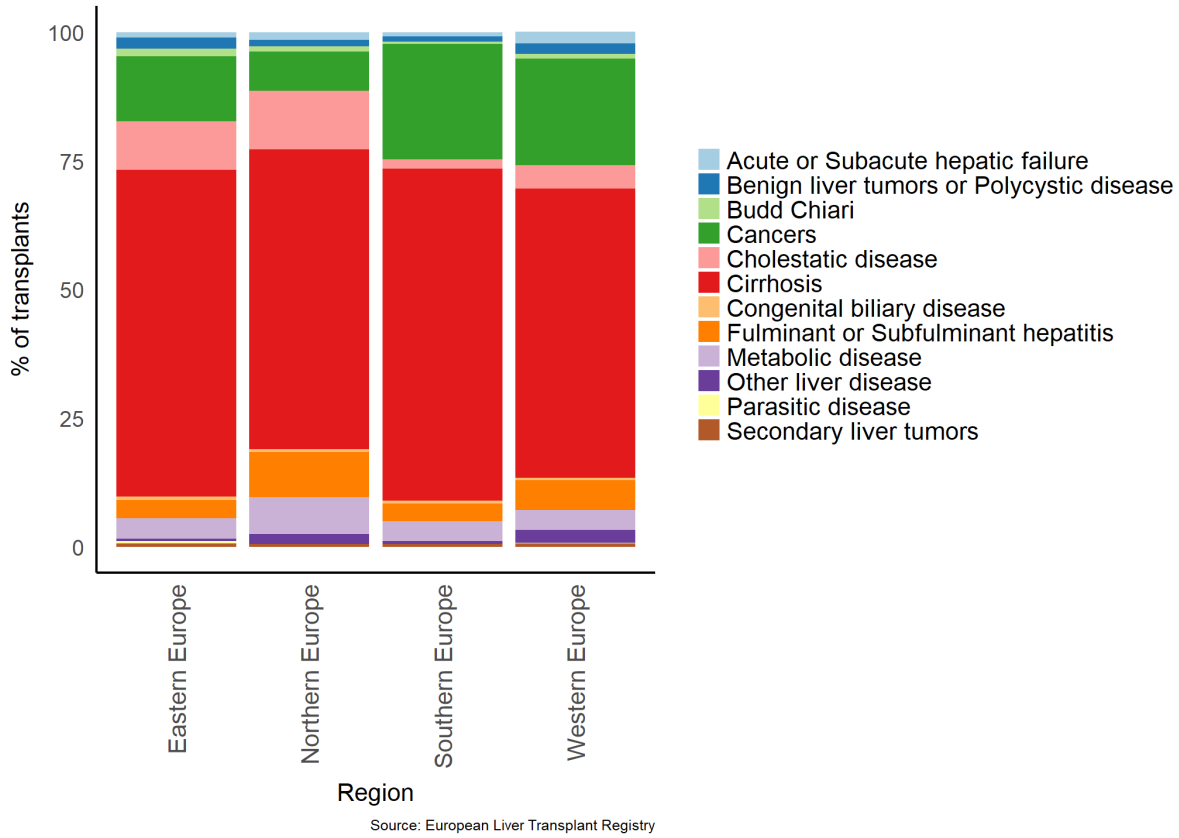


Figure 27. Primary Indication of Liver Transplantation in Europe 01/01/1968-30/06/2017 for all countries

Cyprus, Iceland, Kazakhstan, Latvia, Luxembourg, Malta, Russia and Uzbekistan do not contribute to the ELTR.

Between 1968 and June 2017, the European Transplant Registry (ELTR) recorded 119,512 transplants in both male and female adults. Figure 27 presents the proportion of transplants in participating ELTR countries for each of the four UN sub regions. Cirrhosis was the primary indication for transplantation in all four regions, representing between 56 and 65% of all transplants in Western and Southern European countries, respectively. Cancer was the second most common cause of transplantation for all but Northern European countries, representing 13 to 22% of cancers (Eastern and Southern Europe). In Northern Europe, cholestatic disease represented more than 10% of all transplantations), while fulminant or subfulminant hepatitis represented a larger proportion (9%) of transplants, compared to other regions (ranging between 3 and 5% of transplantations). Other liver diseases, including metabolic disease, benign liver tumours or polycystic disease, Budd Chiari, acute or subacute hepatic failure, congenital biliary disease, secondary liver tumours and parasitic disease make up between 8% of transplants in Southern Europe, to 14% in Northern Europe).

Figure 81 in supplementary material shows the progression over times of the primary disease leading to liver transplantation between 1968 and 2017. Cirrhosis has remained the predominant main disease, followed by cancer, although the proportions of transplantations from cancers has decreased and increased again over time. The proportion of transplants due to metabolic and congenital/cholestatic diseases has increased also over the last 50 years.

Rare and paediatric diseases

There are limited data on rare and paediatric liver diseases in Europe. These conditions, due to their infrequent nature, lead to complications through delayed diagnosis, limited clinical experience or scientific understanding and lack of availability of therapeutic and diagnostic options. Rare diseases while classically defined as a prevalence below 50 per 100,000 of the population can actually present a significant burden to health services, as so many types exist: taken together they affect a high proportion of the population.[16] Data from the ELTR shows that primary and secondary biliary cirrhosis, congenital biliary disease, cholestatic diseases and metabolic liver diseases as rare diseases make up 15.9% of all ELTR-registered transplants between 1968 and 2017. They are often but not always genetic or even monogenetic and so are present in early childhood, yet polygenetic and environmentally induced rare disease, including immune-mediated diseases are increasingly prevalent, and manifest in mid to late adulthood after environmental triggering of genetic predisposition.[17-22]

In childhood diseases, timely diagnosis will optimise for the best outcomes. Evolving technology and personalisation of diagnosis and treatment should offer hope for paediatric and rare liver diseases. In addition, developing treatment pathways, the creation of reference treatment centres and international linked databases should help increase awareness and information on such diseases.

FOCUS BOX – DISCUSSION ON STRENGTHS AND LIMITATIONS OF CURRENT EPIDEMIOLOGICAL DATA

Data on the epidemiological picture of liver disease in European countries is limited in several ways:

- Liver disease is a complex combination of many different diseases and these can be categorised in several ways – including clinical presentation and aetiology or causal risk factor.
- Countries in HEPAHEALTH are not all included in the databases used for this report. For instance Russian mortality data are limited in the WHO European Detailed Mortality Database.
- The GBD project involves modelling using data from neighbouring countries to 'fill in gaps' for conditions and metrics but as a modelling exercise, this is model dependent, relies on high quality input data and has its limitations as it is difficult to replicate and update without large resources.
- Mortality data are based on death certificate recording practices and ICD-10 coding. The quality of recording and the types of recoding vary and data is difficult to compare across countries.
- ICD-10 for liver disease is not helpful for surveillance and epidemiological purposes, with many codes outdated, or not reflecting the aetiology of liver disease. In order to classify liver disease cases according to their causes or risk factors, it is necessary to reclassify individual ICD-10 4-digit codes. Raw mortality data are not available for download for ICD-9 by 4 digit codes, so trends in mortality are limited in time as they cannot go as further back than 1994.
- Hepatitis B and C incidence and prevalence data are collected from countries with varying coverage, using differing case-definitions and from population groups that are often neither representative of the general population, nor include high risk groups.

Recommendations:

- Standardised case-definitions for surveillance and epidemiology – these may be different from clinical diagnosis – should include information on aetiology or cause.
- This may require standardised questionnaires during diagnosis and treatment. Standard recording will allow comparisons within and between countries over time.
- One limitation of changing case-definitions, for liver disease will be the difficulty in comparing with historical data. During a transition period, data should be collected with both old and new case definitions in order to establish the relationship and comparison between old and new data.
- Developing links with surveillance teams in country to encourage scheduled and standardised collection and reporting of mortality and morbidity data.
- Consultation with WHO on the development of ICD-11 codes for liver disease. Use of the same codes in other European-level databases that also present data using ICD-10 or 11 codes. If possible, present 4 digit codes when presenting liver diseases data, as this is the only way that aetiology can be determined.
- Improve hepatitis B and C sero-surveillance – more frequent studies with standard case-definitions covering general population and risk groups.

PART 2. TRENDS IN RISK FACTORS FOR LIVER DISEASE IN EUROPE

Alcohol consumption, obesity, diabetes and viral hepatitis infections are the main modifiable risk factors of liver disease identified in the first part of the report. In order to investigate the impact that these risk factors have had on trends in liver disease, current and historical data for the 35 HEPAHEALTH countries were collected from a range of sources.

Methods

Database data extraction

Alcohol consumption data for European countries was extracted from the WHO Health for All databases. This included current consumption in litres of pure alcohol for total alcohol, beer, wine and spirits.

Obesity prevalence data was obtained from a previous report commissioned from the United Kingdom Health Forum by the World Health Organization[23 24]. This project collected historical national prevalence data from a variety of sources in order to model future trends in overweight and obesity in European countries. This historical input data was used for the HEPAHEALTH project to model past trends in obesity.

Since obesity and diabetes are both related predictors of non-alcoholic fatty liver disease, as well as co-factors in the development and progression of other liver diseases[25], country-level type 2 diabetes prevalence data in adults was obtained for current and past years from the International Diabetes Federation's Diabetes Atlas project.[26]

Information on injecting drug use, as one of the modes of transmission for hepatitis B and C was also collected from the European Monitoring Centre for Drugs and Drug Addiction.[8]

See supplementary material for further details on data sources, data manipulation and analysis.

Literature review

Reviews presenting data on trends in risk factors and their association with liver disease were identified and extracted using a comprehensive literature search strategy - see supplementary material for further information.

Snowballing

As for part 1: The current and historical burden of liver disease in Europe, the sources of information identified were communicated to liver disease experts, in order to collect further information of potentially useful sources.

Qualitative interviews and survey

In order to complement the data collected from published sources and databases, a qualitative interview study was conducted. Experts in the field of liver disease across Europe were contacted and asked to participate in semi-structured, recorded interviews to ask their opinions about trends in liver disease in Europe and their own regions and countries. The interviews discussed what experts thought were the most important determinants of these trends, what barriers exist to good liver health, and what public health priorities should be promoted to improve liver health. A short online survey was also circulated to members of the EASL network. The questions mirrored those asked in the qualitative interviews, and focussed on how trends have changed over time in respondents' countries and the main cause for this, as well as the perceived facilitators of, barriers to, and priorities for good liver health in the respondent's country. A thematic analysis was conducted on the qualitative interviews. Detailed methods and all results can be found in the supplementary material.

Data and discussion

Alcohol consumption and liver disease

Alcohol consumption is an established risk factor for liver disease[27 28], and there is strong evidence that heavy alcohol consumption is associated with a greater risk of liver cirrhosis and liver cancer.

A meta-analysis of observational studies examined the dose response relationship between alcohol and cirrhosis, it considered how the association varied by sex and by cirrhosis endpoint examined (morbidity or mortality).[29] The meta-analysis confirmed previous findings of a strong dose-response relationship between average alcohol consumption and the risk of liver cirrhosis. Consumption over two drinks a day in women and three drinks a day for men was associated with significantly increased risk in cirrhosis morbidity, indicating that women had higher relative risks than men for the same amount of drinking. However, the effect of alcohol consumption was greater for mortality in comparison with morbidity studies for both sexes, as a higher risk of death from liver cirrhosis was estimated for one drink per day on average in women, increasing with increasing volume of alcohol consumption.

Results therefore indicate that no amount of alcohol consumption can be recommended when considering liver cirrhosis and the increased risk of mortality. The smaller effect size on morbidity compared to the larger risk for mortality may indicate that people should abstain after any sign of liver problems, including the possibility of reaction with drugs for liver problems. One limitation of this study is the inability to investigate the issue of binge drinking and alcohol type in the review.

In a systematic review, a linear dose-response relationship was estimated between alcohol consumption and risk of liver cancer, with estimated excess risk of 46% for 50g of ethanol per day and 66% for 100g per day.[30 31]

The European region has the highest levels of per-capita consumption of any other continent.[32] Total alcohol consumption is summarised in the WHO Health for All database as annual total litres of pure alcohol consumed per capita in individuals aged 15+ years. Four groups of countries emerged based on time trends for this consumption:

Increasing trend. Countries that have observed an increase over 45 years, starting from relatively low levels (below 9L per capita in 1970) and increasing in recent years. These include countries from the North and East of Europe, but also Cyprus and Malta (Figure 28).

Decreasing trend. A group of Western and Southern countries, such as France, Italy, Spain, Germany and Switzerland as well as Slovenia and Slovakia where annual alcohol consumption has significantly decreased over recent decades. The majority started at high levels of per capita annual consumption (above 10L for Greece and as high as 22L in France in 1970), but have now decreased to levels between 8 and 12L per capita in 2015, see Figure 29.

Stable high trend. A group of countries from across Europe have experienced limited variation in alcohol consumption over time, with levels remaining between 10 -17L per capita, see Figure 30.

Stable low trend. Similarly, a group of countries have observed fluctuating tends over the past 40 years, but have generally stable alcohol consumption at low levels (on average below 10L pure alcohol per person annually). These include Eastern countries such as Bulgaria, Kazakhstan, Serbia and Uzbekistan, but also Netherlands, Sweden and Norway (Figure 31).

It should be noted that alcohol use is prone to measurement bias, underreporting, and bias in the selection of samples for estimating intake, leading to uncertainty in estimates: a recent Organisation for Economic Co-operation and Development (OECD) report states that consumption is known to be under-recorded, with an estimated 11% of alcohol not recorded in OECD countries.32

Furthermore, although these trends are seen at national levels, alcohol consumption patterns are clustered within populations: 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 OECD.[32] Demographic patterns in alcohol consumption are changing too: consumption by younger people is growing, with age of taking up drinking decreasing, as well as an increasing in women consuming alcohol. Patterns of drinking, including drinking frequency and type of alcohol consumed, have differential effects on mortality and risk of disease, with average alcohol consumption and drinking frequency having different effects, as well as the type of alcohol consumed.[33]

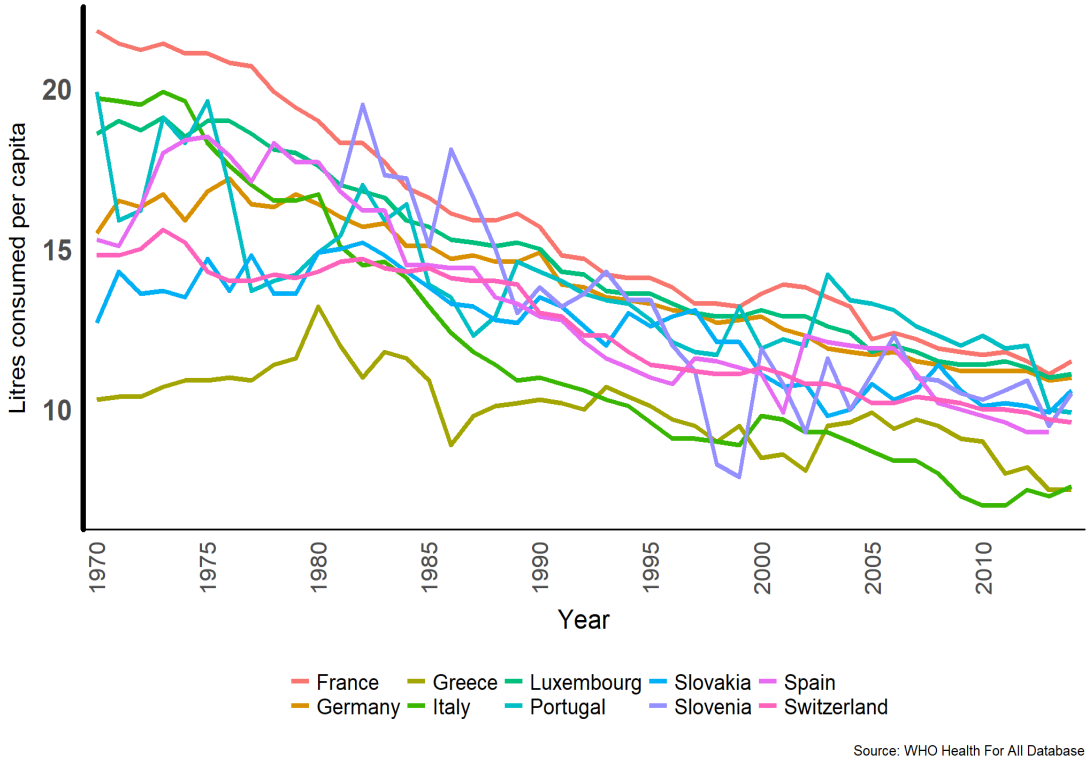


Figure 28. Total consumption of alcohol in countries with an decreasing trend for ages >15y

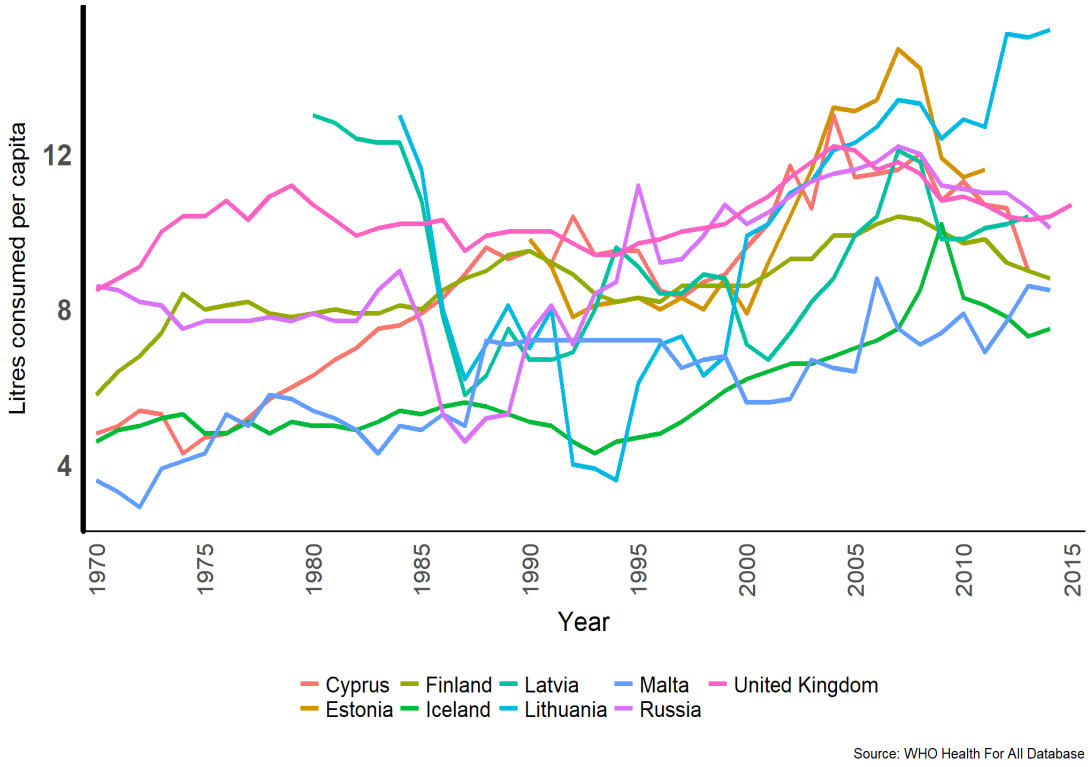


Figure 29. Total consumption of alcohol in countries with an increasing trend for ages >15y

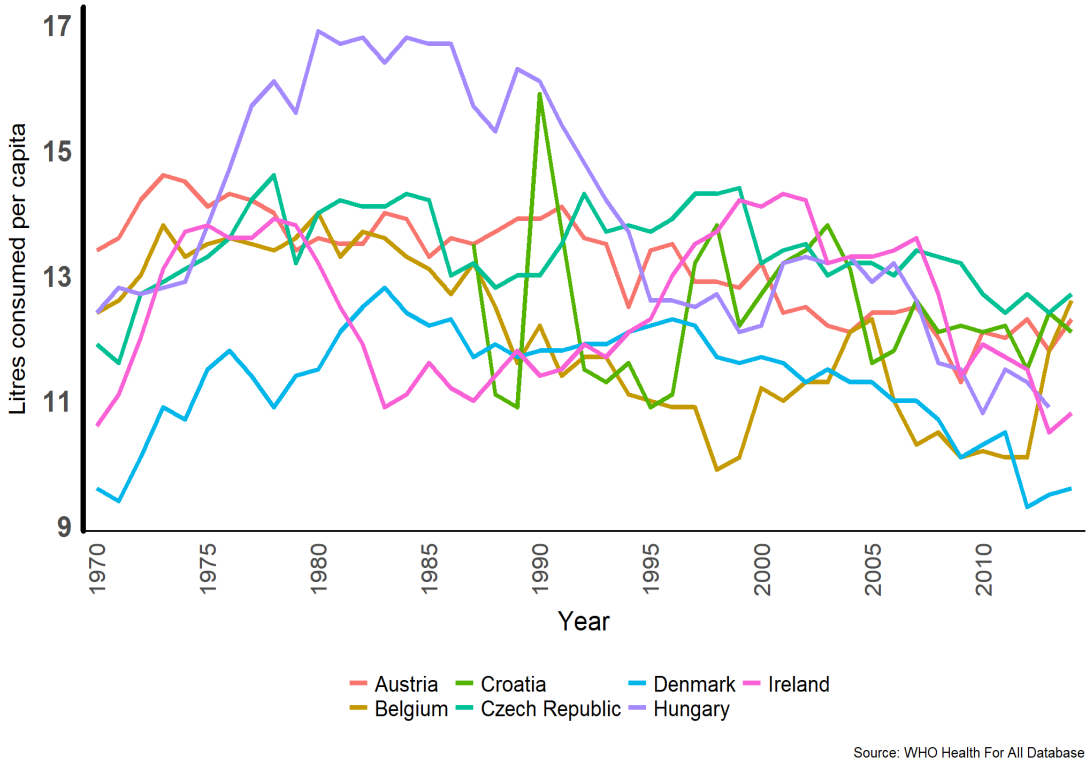


Figure 30. Total consumption of alcohol in countries with stable trend (high consumption) for ages >15y

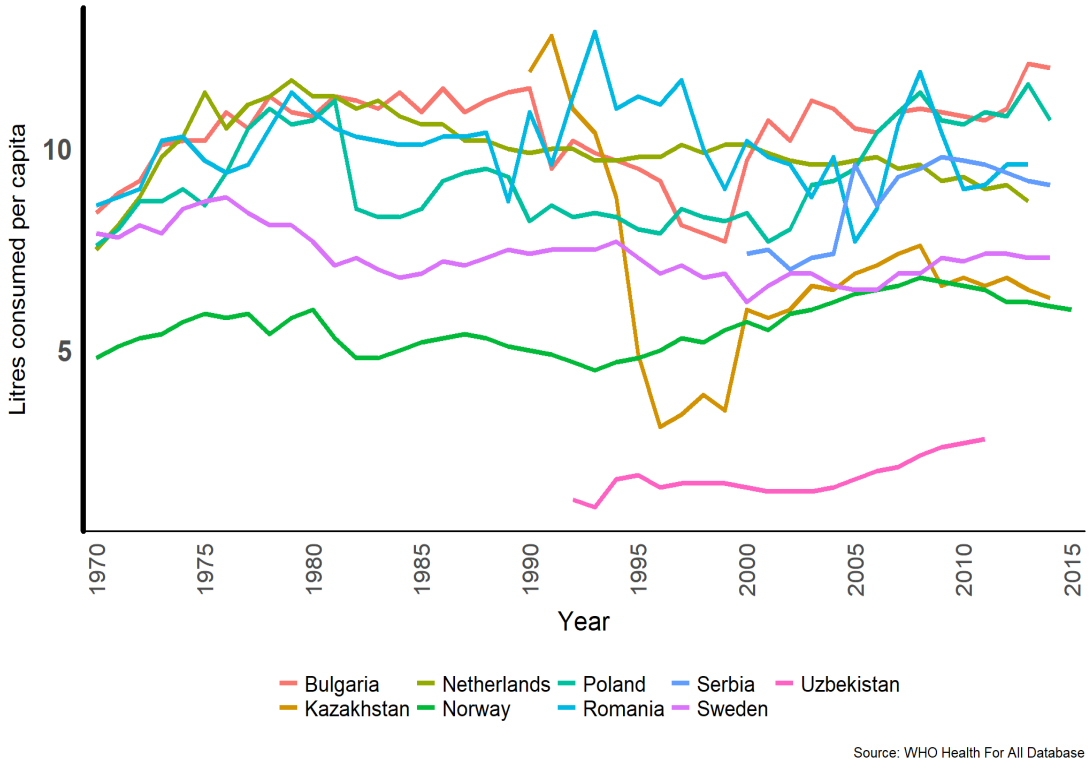


Figure 31. Total consumption of alcohol in countries with stable trend (low consumption) for ages >15y

Pure total alcohol consumption can be broken down by type of alcohol, in the WHO Health for All database. Variations in the types of alcohol consumed goes some way to explaining different patterns in alcohol consumption and liver disease morbidity and mortality, as shown in the figures below. Figure 32 presents the relative contribution of beer, wine and spirits in the United Kingdom, a country with an increasing trend in total alcohol consumption over time. Wine consumption has grown for both genders since 1970 in the United Kingdom, with a recent sharp increase starting in the late 1990s. An equivalent increase in mortality from chronic liver disease and cirrhosis and alcoholic liver disease is shown when superimposing these over the increasing alcohol consumption trends for the United Kingdom (Figure 33). The correlation is similar to those from Razvodovsky *et al.'s* (2014)recent analysis of liver cirrhosis mortality and alcohol consumption in Russia, where similar correlation exist since 1970.[34]

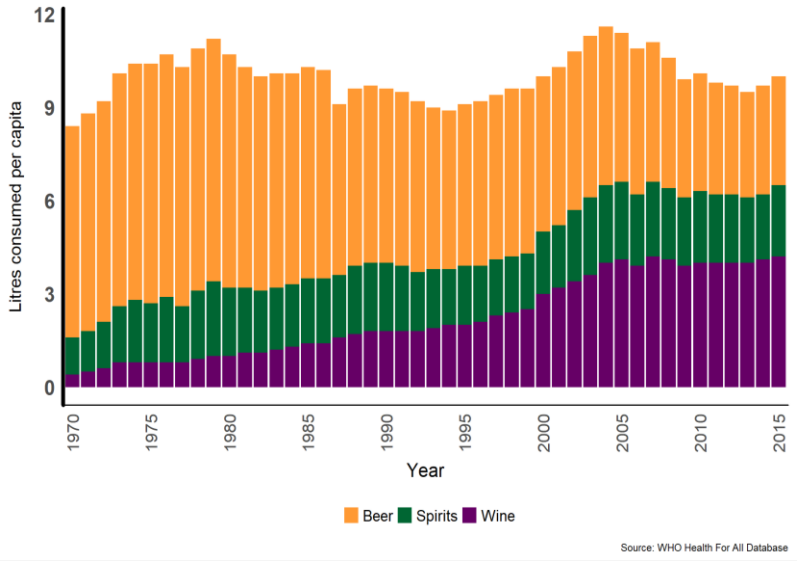


Figure 32. Total consumption of alcohol by type of alcohol ages >15y in the United Kingdom

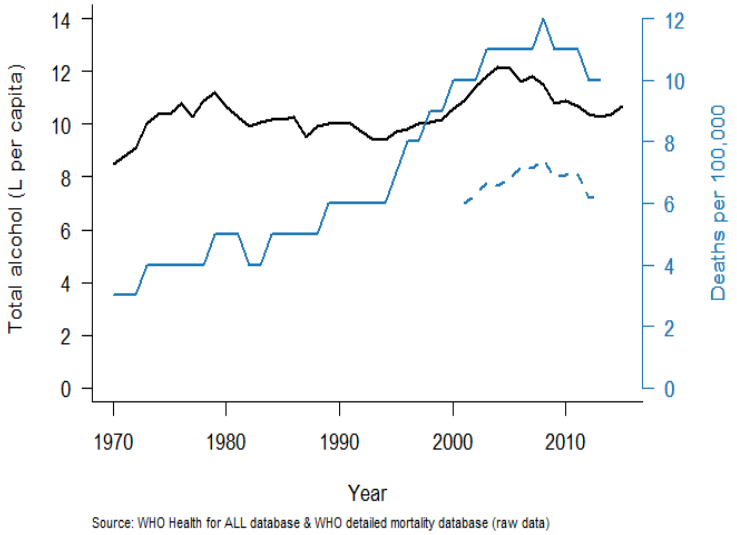


Figure 33. Alcohol consumption (black line) and age-standardised mortality from cirrhosis and chronic liver diseases (blue filled line) and alcoholic liver disease mortality (blue dashed line) in the United Kingdom

Conversely, in countries such as France, where decreasing alcohol trends are in a large part due to lower consumption of wine (Figure 34), a matching reduction in alcoholic liver disease and chronic liver disease and cirrhosis has been observed over the last decades (Figure 35).

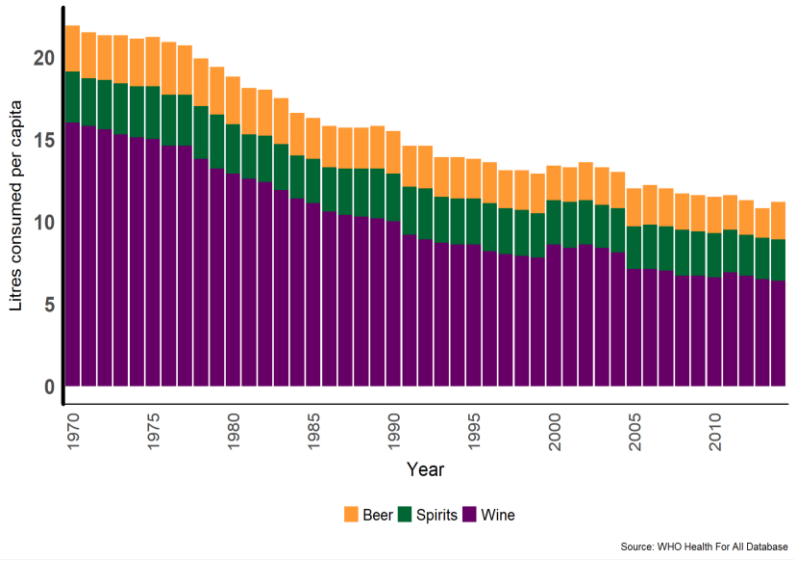


Figure 34. Total consumption of alcohol by type of alcohol ages >15y in France

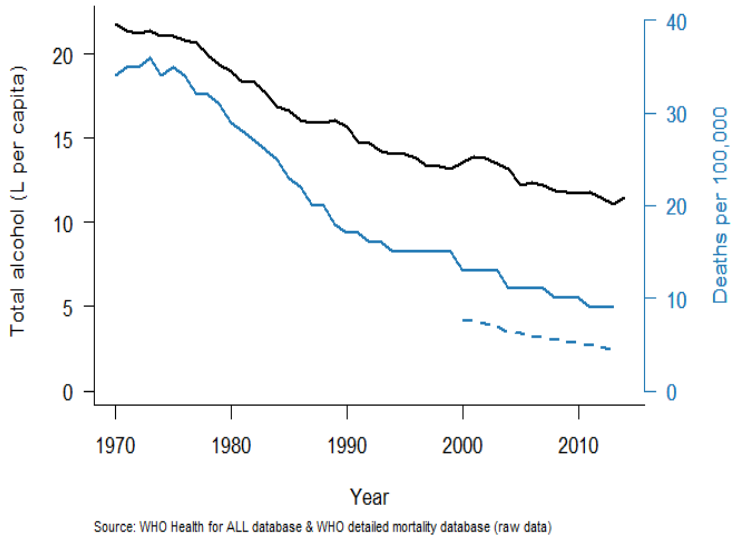


Figure 35. Alcohol consumption (black line) and age-standardised mortality from cirrhosis and chronic liver diseases (blue filled line) and alcoholic liver disease mortality (blue dashed line) in France

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 (Figure 36), or Sweden which has remained at a relatively stable level over 40 years (Figure 38).

In the Czech Republic, overall cirrhosis and other chronic liver disease mortality remains stable, but more granular data available using ICD-10 coding shows an increase in alcoholic liver disease.

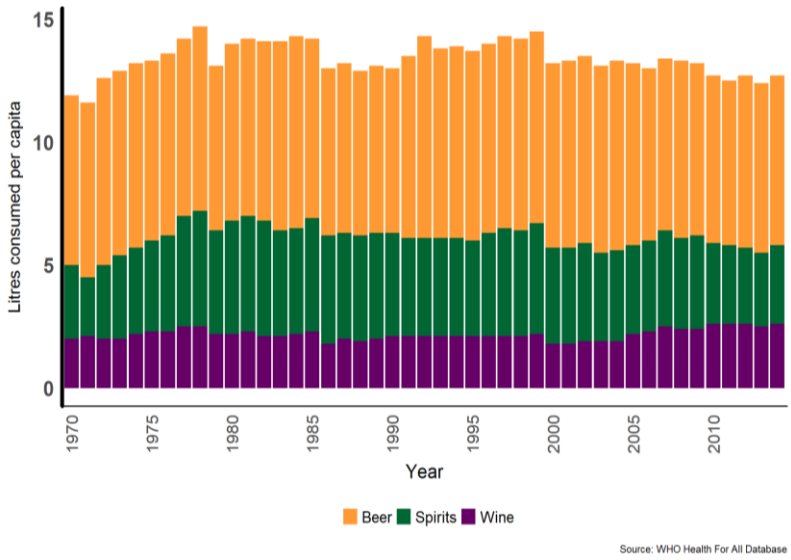


Figure 36. Total consumption of alcohol by type of alcohol ages >15y in the Czech Republic

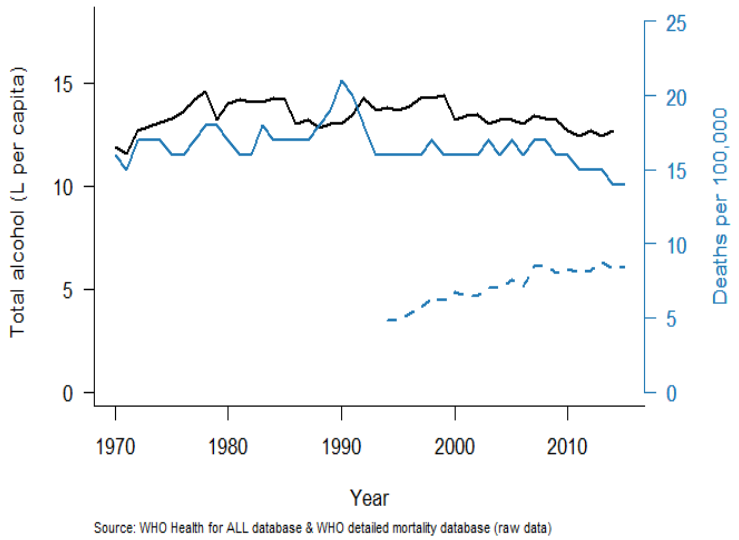


Figure 37. Alcohol consumption (black line) and age-standardised mortality from cirrhosis and chronic liver diseases (blue filled line) and alcoholic liver disease mortality (blue dashed line) in the Czech Republic

In Sweden, although total alcohol consumption is stable, there have been shifts in the types of drink consumed, with a clear decrease in beer and spirits and an increase in wine consumption up to 2014. The steady increase in mortality from liver disease appears to mirror the increase in wine consumption, while total intake appears to be stable but relatively low in Sweden, see Figure 39.

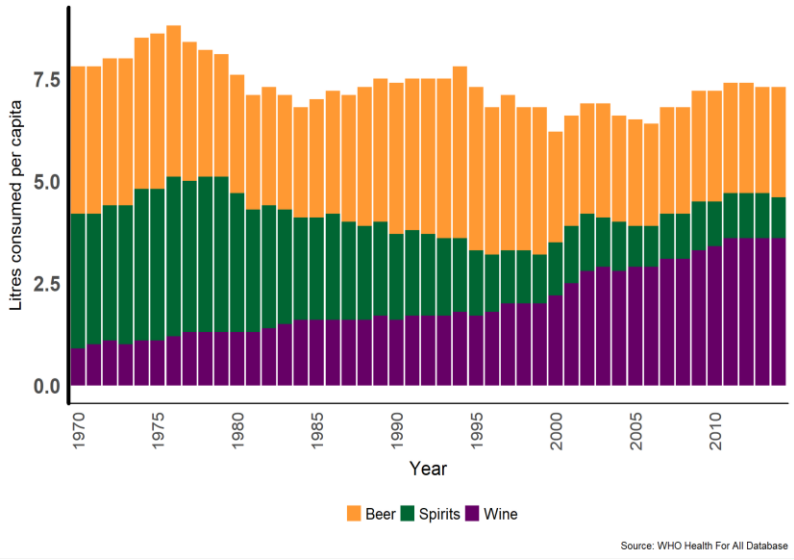


Figure 38. Total consumption of alcohol by type of alcohol ages >15y in Sweden

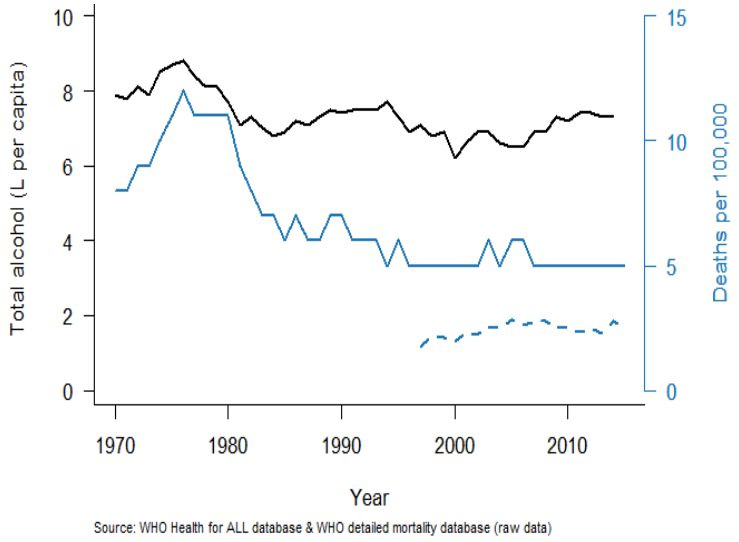


Figure 39. Alcohol consumption (black line) and age-standardised mortality from cirrhosis and chronic liver diseases (blue filled line) and alcoholic liver disease mortality (blue dashed line) in Sweden

Obesity and liver disease

Obesity and excess central adiposity especially, are risk factors for NAFLD. For every one unit increase in Body Mass Index (BMI), the odds of forming NAFLD increase by 13 to 38% and per 1cm increase in waist circumference, they increase by 3 to 10%[35] As well as being a risk factor for non-alcoholic liver disease, excess body weight is a co-factor for the progression of liver disease from all aetiologies.[36]

The prevalence of obese people (% of total population with a BMI greater than 30kg/m^2) was collected from national surveys. The most recent data for each country shows variation, ranging from below 10% of the total adult population in Norway, Italy and Switzerland, to above 25% in Uzbekistan and the United Kingdom for females with a similar pattern for males, Figure 40.

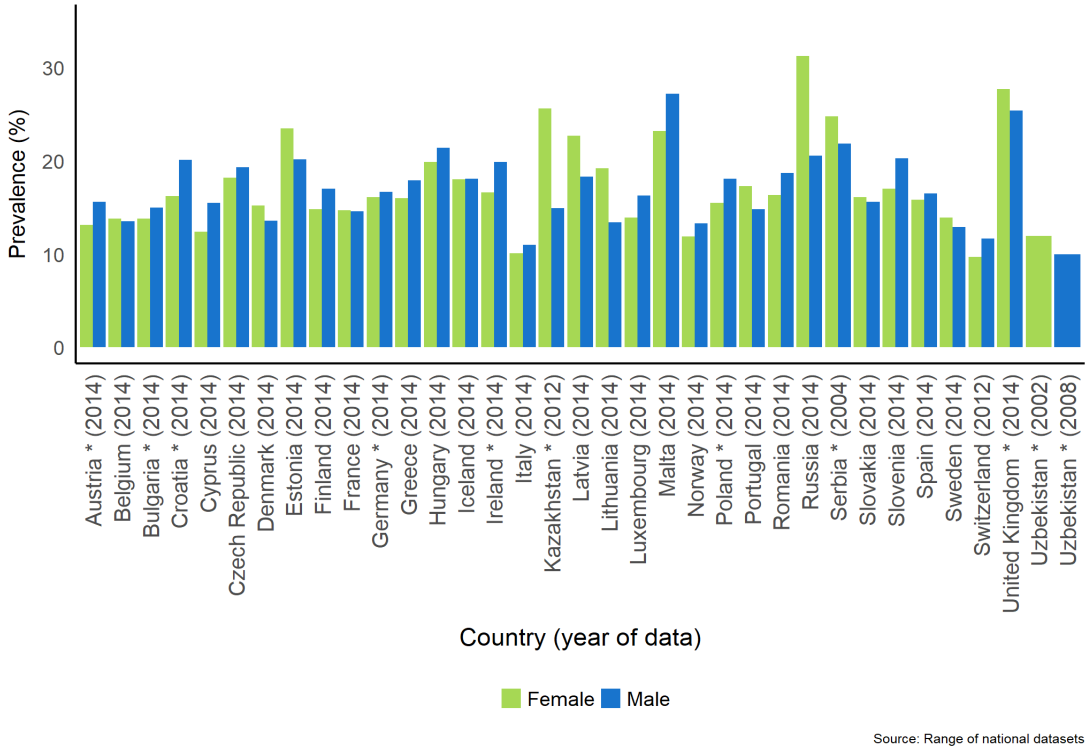


Figure 40. Prevalence of obesity (BMI>30kg/m^2) in Females and Males in the most recent year available

* 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.

Across all regions of Europe, countries have seen an increase in average BMI in the population, albeit at different rates, in both males and females. For trajectories in obesity prevalence over the last 15 years in the four European sub regions see Figure 41, Figure 43, Figure 45 and Figure 47 below,. Variations, showing slight peaks and troughs may be due to the use of multiple different surveys in some countries, for which methodologies and samples vary. 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.[37 38] Nevertheless, the increase 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.

Below each region's BMI prevalence trajectories are overlaid data of prevalence and mortality from liver cancer and NAFLD for one country taken from each of the four regions, which highlight this effect and indicate that while some countries are shifting towards greater rates and an epidemic of obesity, the future is likely to involve a corresponding NALFD-epidemic, see Figure 42 for Estonia as an example for Northern Europe, Figure 44 of Romania representing Eastern Europe, Croatia as an example of a country in Southern Europe in Figure 46 and Belgium in Figure 48 showing the overlay of obesity prevalence and mortality of liver diseases for Western Europe.

Northern Europe

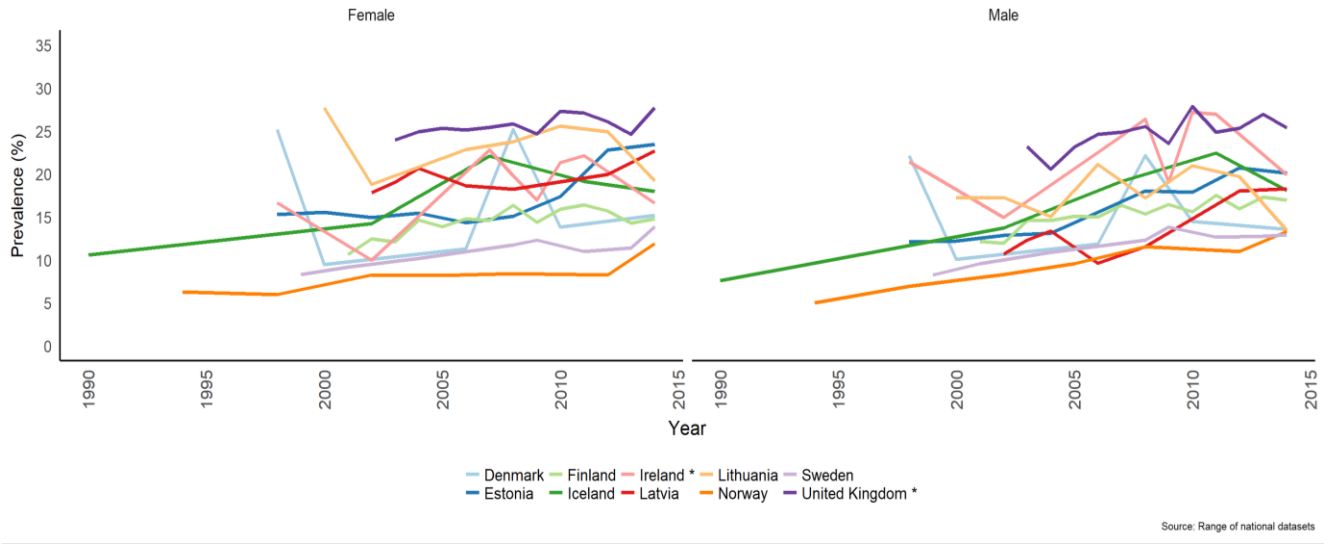


Figure 41. Prevalence of obesity (BMI>30kg/m^2) by gender in adults > 20y in Northern European countries

* Ireland (2007 to 2010) and all United Kingdom data points used measured BMI. All other data points used self-reported.

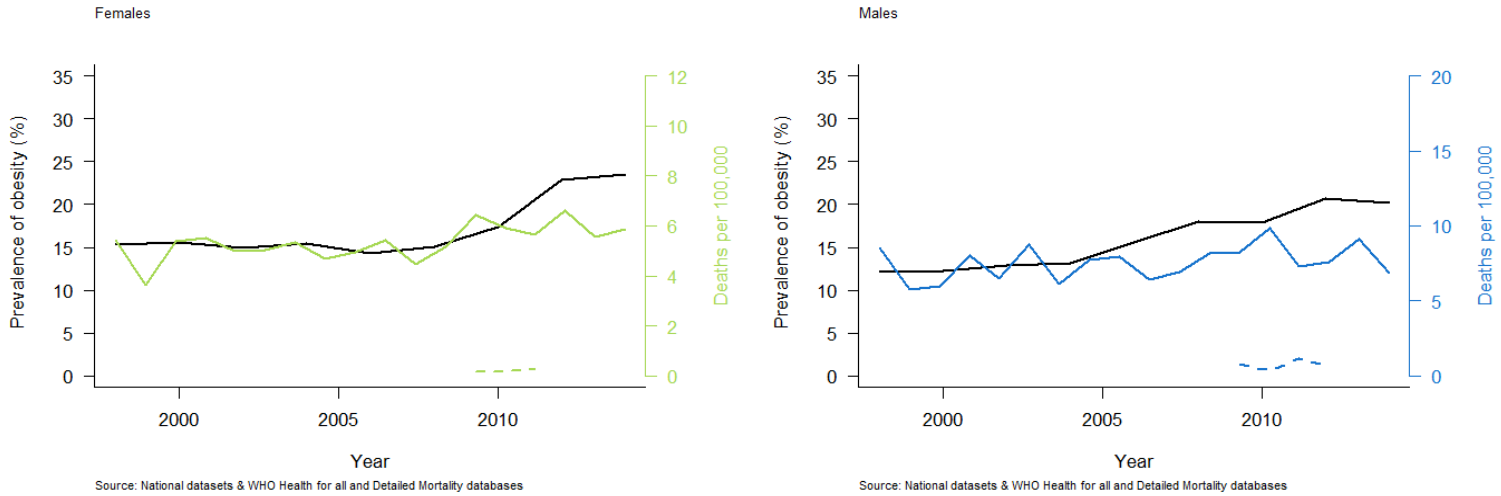


Figure 42. Obesity prevalence (black line) and age-standardised mortality from liver cancer (coloured line) and NAFLD (coloured dashed line) in Estonia (all ages)

Eastern Europe

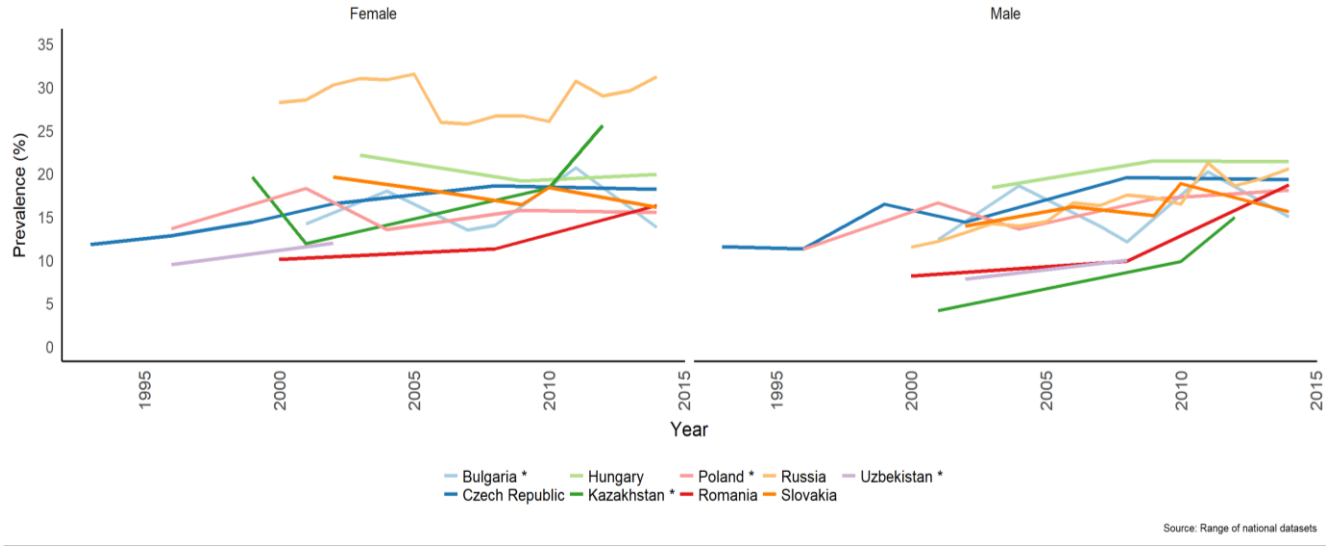


Figure 43. Prevalence of obesity (BMI>30kg/m^2) in Females and (> 20 y) in Eastern European countries

* Bulgaria 2011, Kazakhstan 1999 and 2012, Poland 1992 and 2001, Uzbekistan 1996 and 2002 data points use measured BMI. All other data points used self-reported.

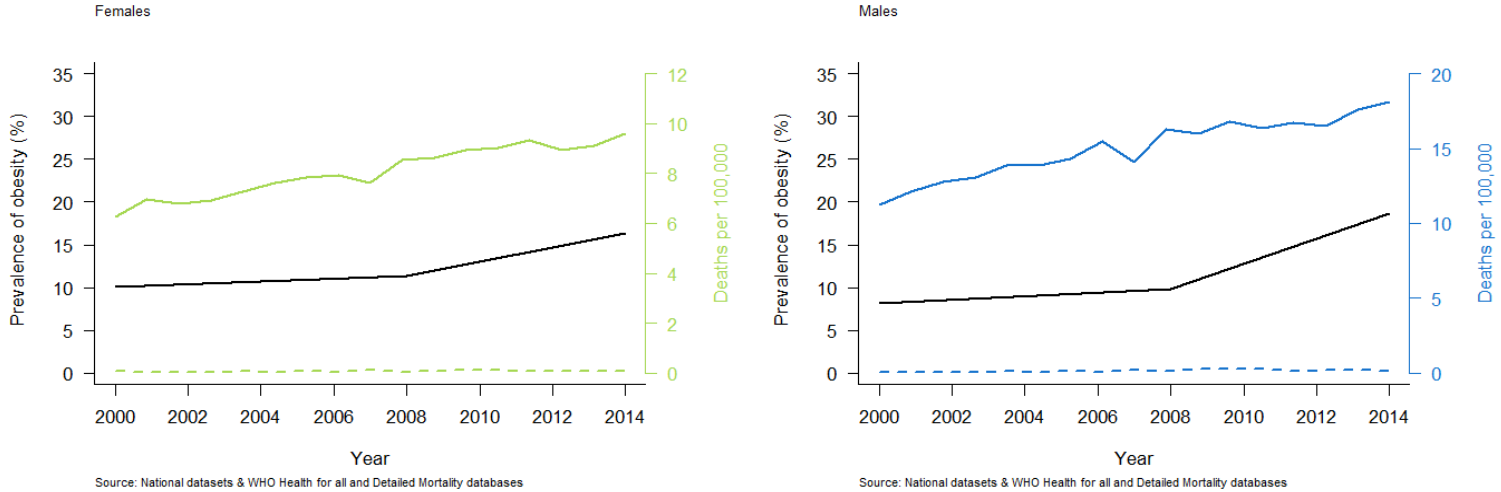


Figure 44. Obesity prevalence (black line) and age-standardised mortality from liver cancer (coloured line) and NAFLD (coloured dashed line) in Romania (all ages)

Southern Europe

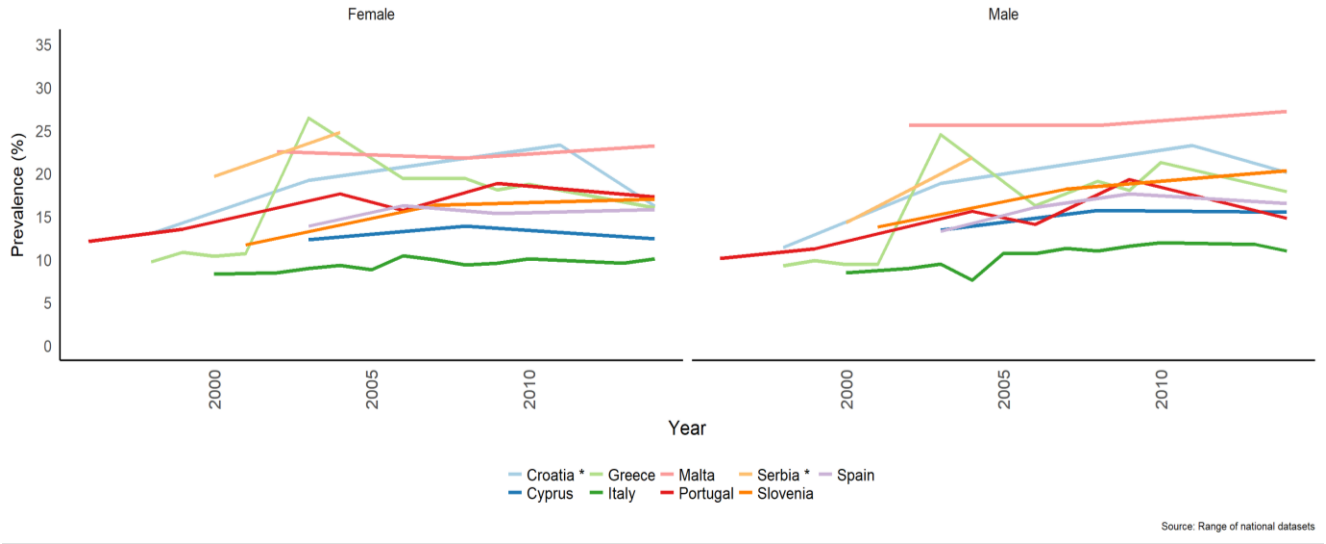


Figure 45. Prevalence of obesity (BMI>30kg/m^2) in Females and (> 20 y) in Southern European countries

* All Croatia and Serbia data points use measured BMI. All other data points used self-reported.

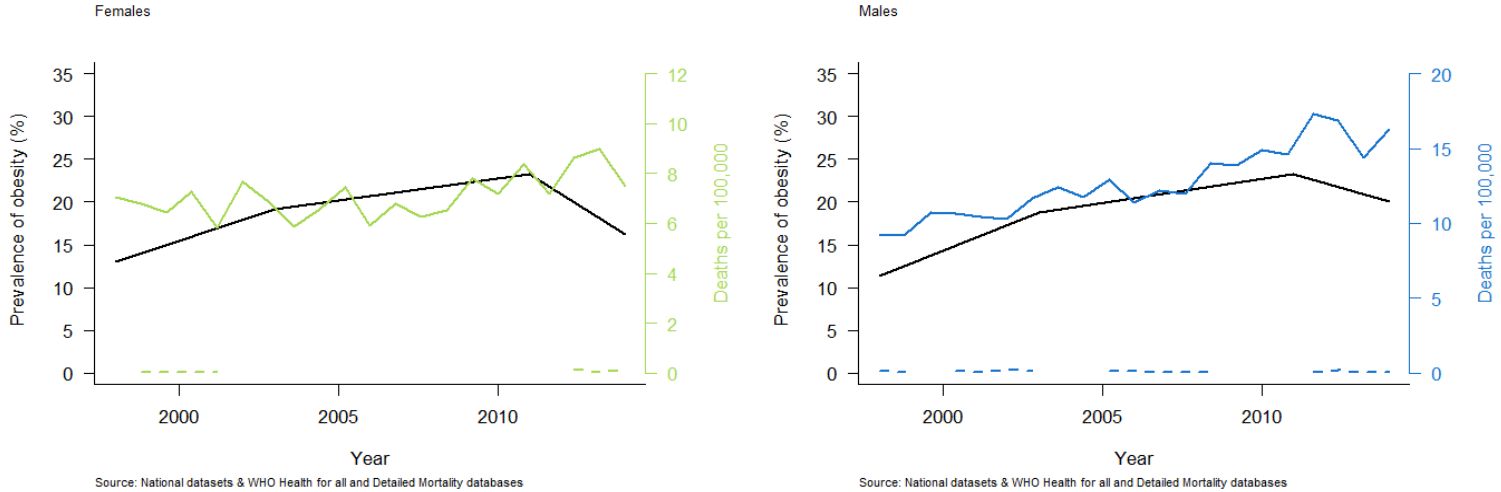


Figure 46. Obesity prevalence (black line) and age-standardised mortality from liver cancer (coloured line) and NAFLD (coloured dashed line) in Croatia (all ages)

Western Europe

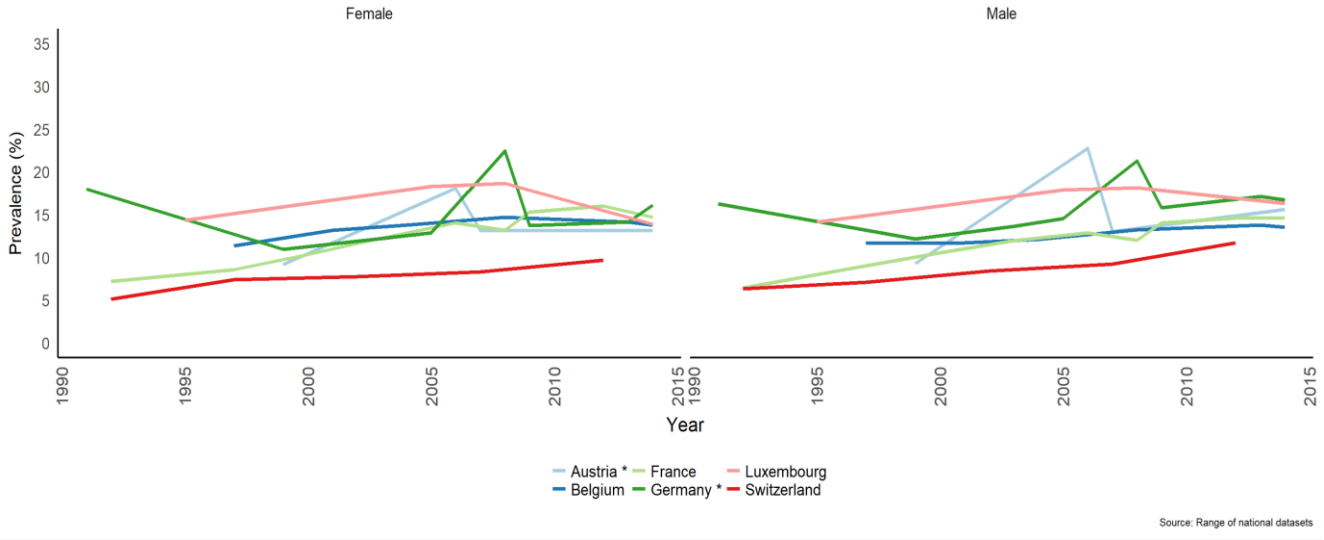


Figure 47. Prevalence of obesity (BMI>30kg/m^2) in Females and (> 20 y) in Western European countries

*Austria 2012, Germany 1991 and 2011 data points use measured BMI. All other data points used self-reported.

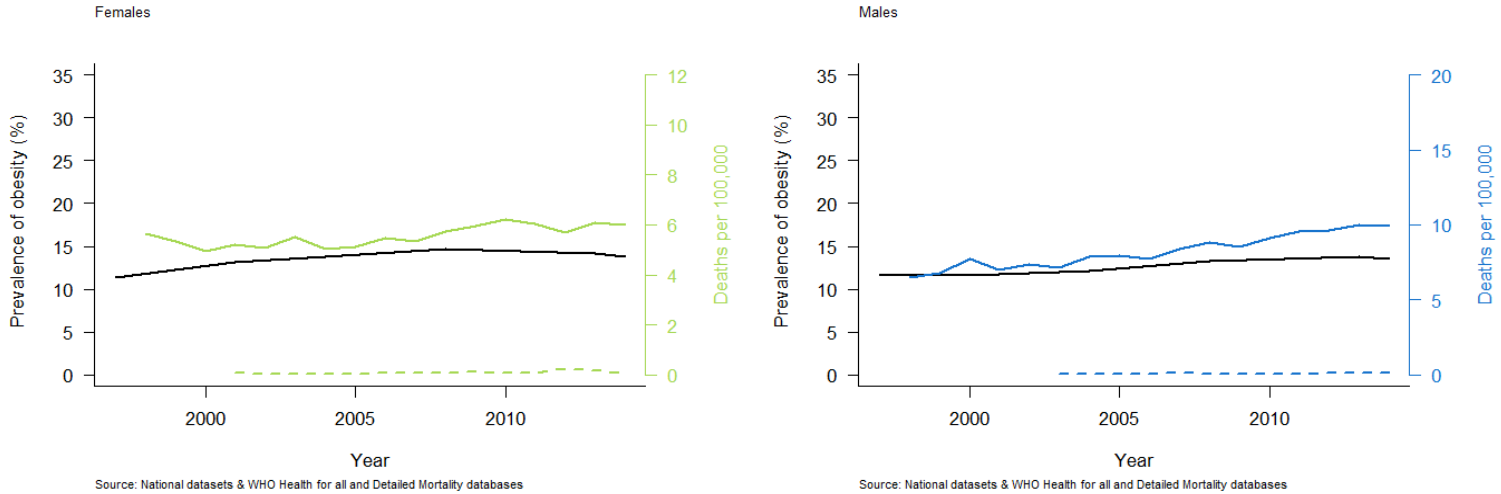


Figure 48. Obesity prevalence (black line) and age-standardised mortality from liver cancer (coloured line) and NAFLD (coloured dashed line) in Belgium (all ages)

Diabetes and liver disease

Diabetes type 2 is a risk factor for the development of cirrhosis in individuals infected with hepatitis C,[39] as well as liver cancer in cirrhotic patients.[40] The International Diabetes Federation collects national-level diabetes prevalence in their Diabetes Atlas for several years. In 2015, European countries range from <4% of the total population with diabetes type 2, to countries such as Serbia with more than 10% of individuals diagnosed with type 2 diabetes (Figure 49).

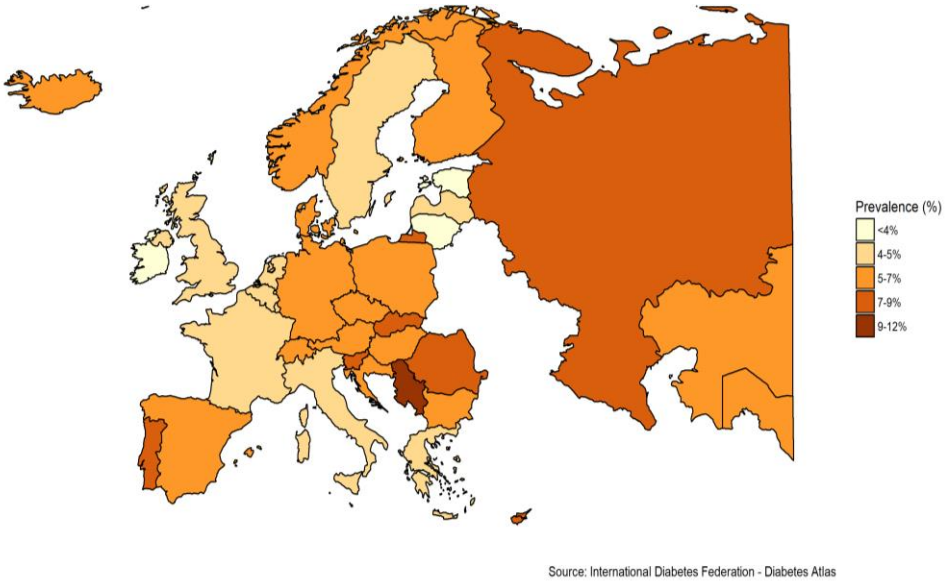


Figure 49. Map of the age-adjusted prevalence of type 2 diabetes in adults, both genders (2015)

Time trends in the prevalence of adult type 2 diabetes in countries, by region, are shown in Figure 50. Data by age was not available before 2007. Data prior to this date are shown in the supplementary materials section, but this data was not age standardised, simply aggregated across all ages 20-79. The International Diabetes Federation changed their methodology for estimating prevalence in 2011[41], which may explain the shifts in prevalence in that year, see further details in supplementary material.

Northern European countries all showed a trend towards increasing prevalence of type 2 diabetes in adults, except Lithuania and Latvia, where prevalence decreased from 2011 onwards.

Similarly for Eastern Europe, prevalence decreased between 2011 and 2013 in all countries but Slovenia and the Czech Republic, but all countries have experienced a recent increase between 2013 and 2015, to prevalence between five and eight percent of the population.

In Southern Europe, prevalence was increasing for majority of countries, except for Croatia Greece and Italy, between 2007 and 2015.

Diabetes prevalence levels have generally remained stable in Western European countries, except for Germany where a sharp decrease followed by an increase was seen in recent years.

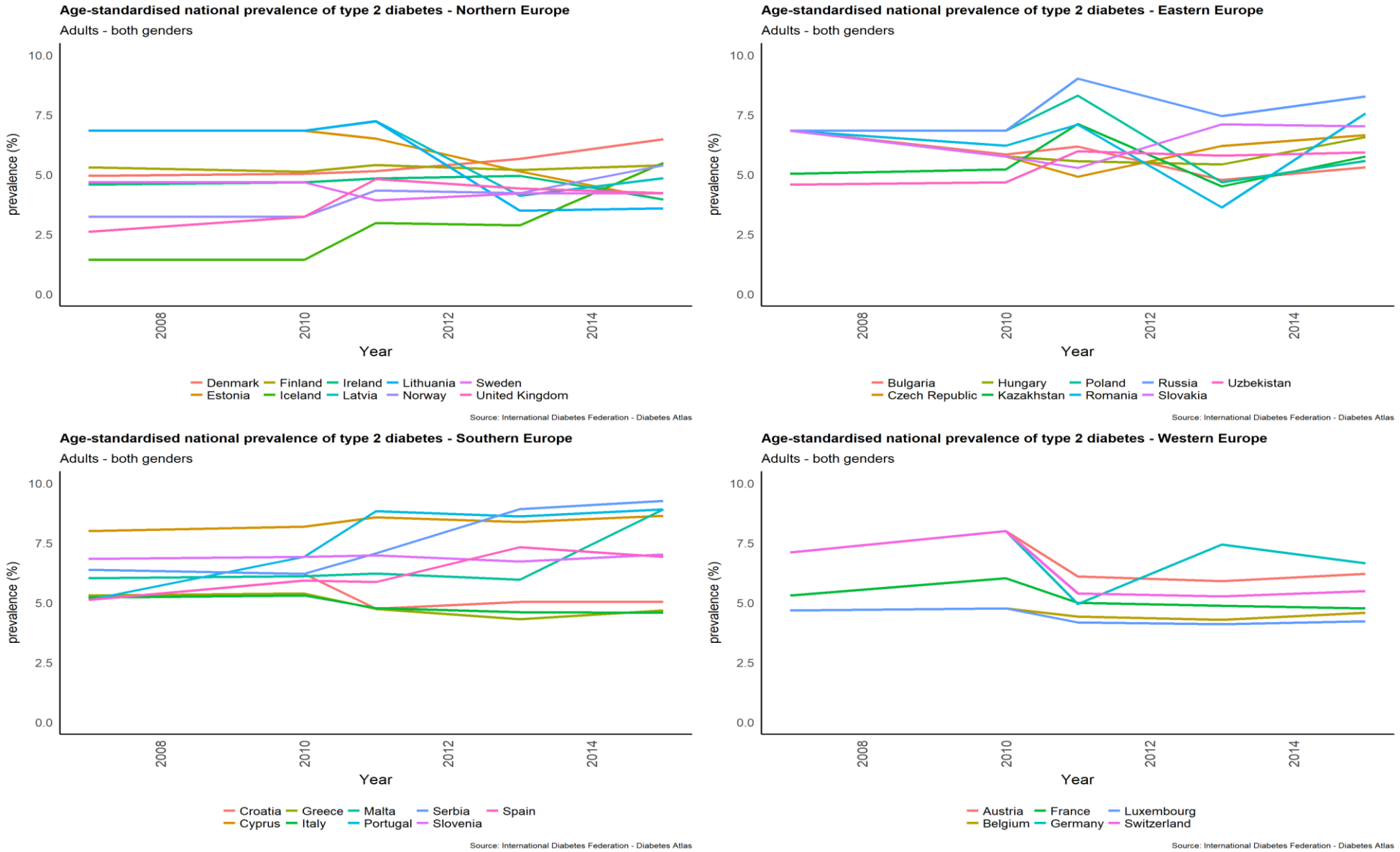


Figure 50. Age-standardised prevalence of type 2 diabetes in adults aged 20-79 years over time

Note: Estimation methodology was revised in 2011

Injection drug use

Common routes of transmission for the blood-borne hepatitis B and C include intravenous drug use, reuse of needles in healthcare settings and transfusions/haemodialysis. In addition, sexual transmission of hepatitis B is increasingly important in Europe, while vertical and horizontal mother-to-child transmission mainly occur in areas of high endemicity, as well as transmission during medical, surgical or tattooing procedures for hepatitis B.[42-44]

Injection drug use is an important risk factor for viral hepatitis infection, in particular hepatitis C. Estimates of anti-hepatitis C prevalence amongst PWID has been shown to be almost 50 times higher than in the general population, in countries where data were available.[45] A recent review from 2007-2014 found seven papers that reported on the burden of disease or mortality related to hepatitis C infection amongst PWID in the European Union.[46] These included four observational studies, two modelling studies and one cost-effectiveness study, with study settings varying from single centre to nationwide. The crude all-cause mortality ranged from 2.1-12 cases / 100person-years. There were variations in the crude mortality rates for those with chronic hepatitis C and spontaneous resolvers, ranging from comparable rates to a greater than 4-fold difference. Two studies reported liver-related crude mortality rates of 0.11 and 3.0/100person-years.[47 48]

PWID prevalence from the EMCDDA was available for 16 countries and ranged from 0.02% in Spain, to 0.92% in Latvia. The Czech Republic and Estonia had the next highest PWID prevalence rates at 0.63% and 0.60%, respectively (Figure 51).

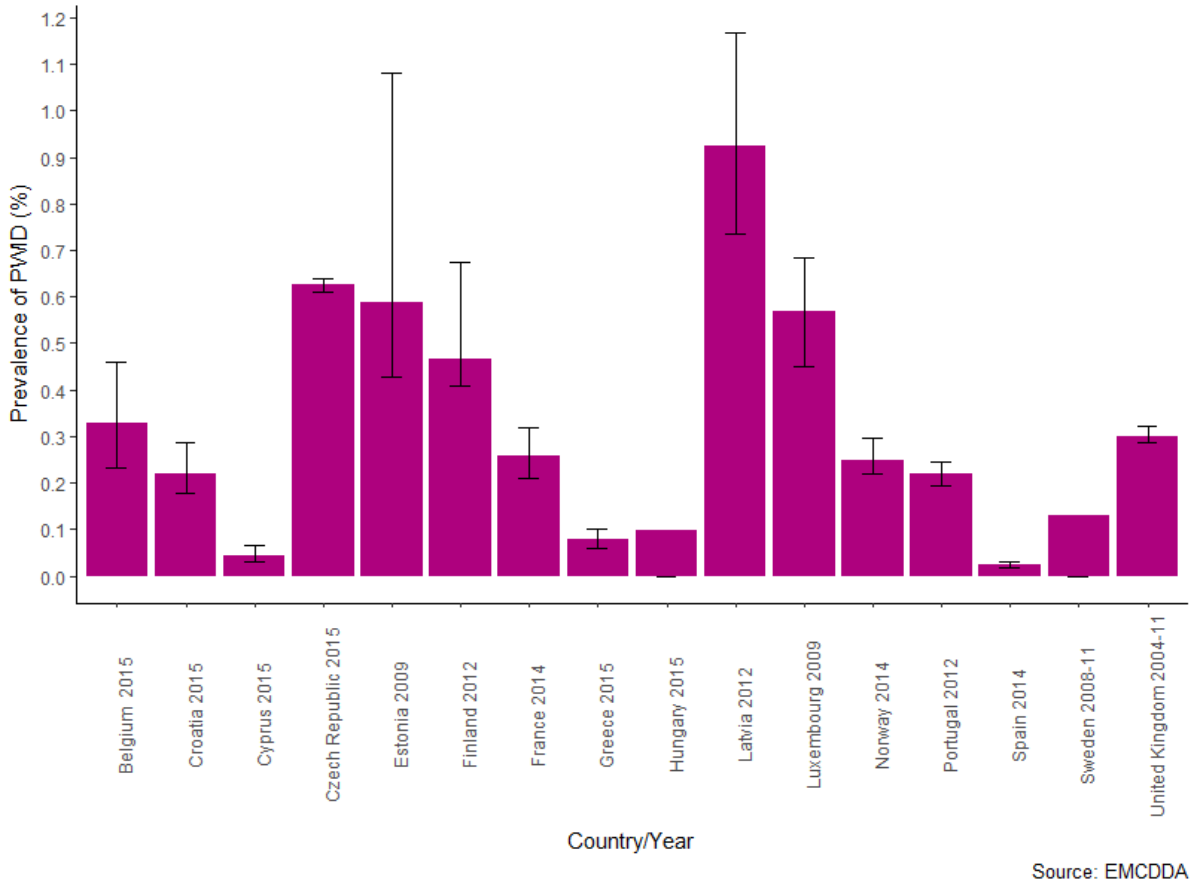


Figure 51.Prevalence of PWID in European countries

Variations in the prevalence of the use of injecting drugs may be one pattern explaining the variations in prevalence of hepatitis B and C in the general population, although as mentioned in part 1, accurate estimation of viral hepatitis prevalence is limited by a range of biological, demographic and surveillance factors. The EMCDDA report that HBsAg prevalence among PWID ranged from 0% in Croatia to 11% in Spain among the 21 countries. Norway, Ireland, France and Germany had an estimated HBsAg prevalence <1% among PWID, whereas Lithuania and Romania had almost as high a prevalence as Spain at 10.5% (Figure 52).

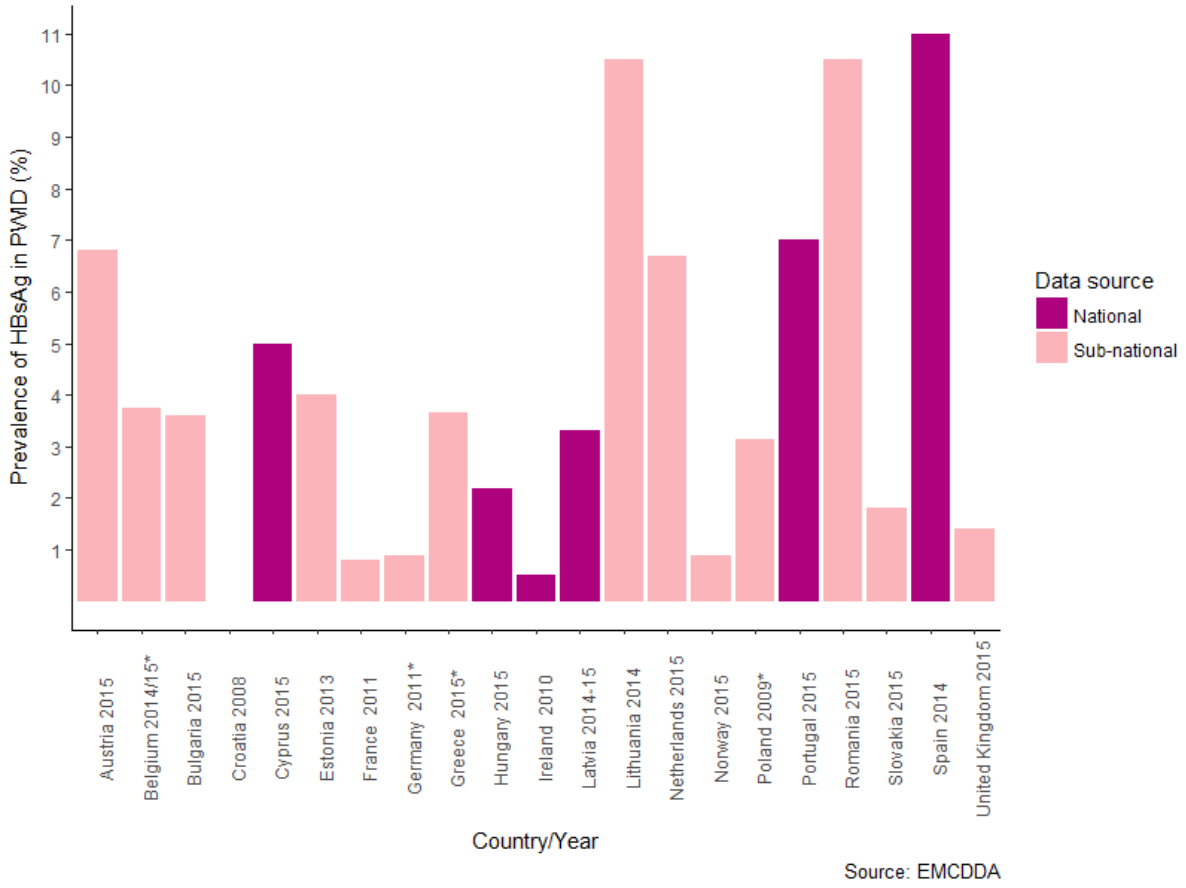


Figure 52. Prevalence of Hepatitis B infection in PWID

* Estimates are mid-point from a range of estimates. Croatian estimate from subnational source.

Twenty-eight countries had data available on hepatitis C virus antibody prevalence in PWID from the EMCDDA, (see Figure 53). The prevalence of hepatitis C virus antibodies among PWID was lowest in Austria (26.8%) and the Czech Republic (15.7%) and highest among Sweden (96.8%) and Portugal (83.5%).

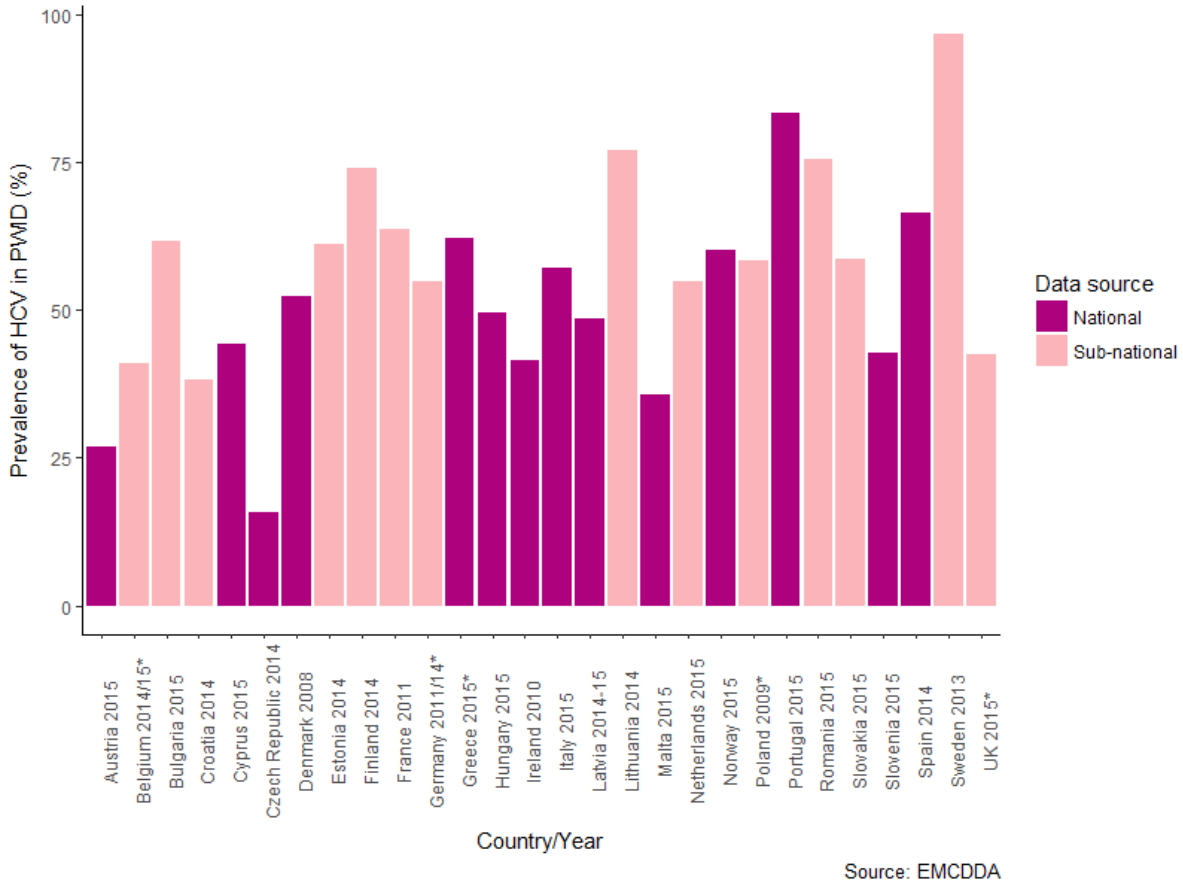


Figure 53 Prevalence of Hepatitis C infection in PWID

* Estimates are mid-point from a range of estimates.

FOCUS BOX – RESULTS FROM QUALITATIVE EXPERT INTERVIEWS

Seven European liver disease experts were interviewed and seven others participated in focus group using a semi-structured questionnaire. Thematic framework analysis grouped responses into four main themes. See supplementary material for detailed methods and results.

Trends in liver disease in Europe

Respondents noted different patterns in liver disease across countries. While Western and Southern European countries highlighted the emergence of alcoholic and non-alcoholic liver disease, the main focus for many Eastern European respondents was still the burden of hepatitis B and C infection. Interviewees related these patterns to differences in behaviour and exposure to risk factors.

"There are some differences between North and South [country]. It's a small country, but there are some differences. We have, for example, more hepatitis B and more hepatitis C in the south. Um, alcohol very rightly, slightly higher in the north".

These different patterns led differing effects for various population groups:

"Alcoholic liver disease and viral hepatitis are very highly clustered. Not only in areas of deprivation because there's a very strong linkage with health inequalities"

"we also need to be looking at specific populations which are most likely to be affected with viral hepatitis and the classic groups there are if you like the baby boomer generations"

Barriers to good liver health in European countries

- Alcohol consumption
- Obesity, diabetes and the metabolic syndrome**:** *"If you have diabetes plus obesity these conditions do increase the risk of hepatocellular carcinoma which is something very new"*
- Drug use
- Late-presentation and low awareness of liver disease
- Medical systems capacity and training
- Screening and diagnostics
- Government and policy
- Industry

"We have a very powerful drinks industry. They're very well organised. They've learnt an awful lot from tobacco regulation"

Future priorities

The priorities in the fight against liver disease, which were mentioned most frequently by respondents, included:

- Diversifying liver disease expertise: Early diagnosis and the future role of the GP
- Improving public awareness: Educating governments and populations of the diverse causes of liver disease and the rising morbidity and mortality it accounts for.
- Treatment and policy action: Improving diagnostic tools, access to vaccines and implementing target policies, such as taxation can help transform the burden of liver disease.

The following expert **recommendations and thoughts** were noted**:**

The liver doesn't have any pain receptors, there are little to no symptoms of liver disease and reliable tests for various types of liver disease do not exist. Therefore reducing the burden of liver disease requires a paradigm shift in how diagnosis, treatment and prevention are enacted. Some suggestions include reducing the stigma of liver disease, educating GPs, early diagnosis, and enacting targeted policy

"We really are in a poor position. But the only advantage of that is that things sort of can only get better really. They're going to get worse first unfortunately

CASE STUDY: LIVER DISEASE AND RISK FACTOR DATA IN ITALY AND IN FINLAND

The aim of these case studies was to showcase the data available in the database as presented in parts 1 and 2 of the review, by providing an in depth case study for two countries (Italy and Finland) where trends can more clearly be seen and analysed.

These case studies serve to demonstrate the use of the epidemiological and risk factor data collected as part of the HEPAHEALTH study, by highlighting the key analyses and plots which can be conducted. Trends and the wider societal context were analysed to help develop a rich picture of liver disease mortality, prevalence and associated risk factors in Italy.

Case study: Liver disease and risk factor data in Italy

Summary of overall findings

- **Historic trends in mortality chronic liver disease and cirrhosis** indicate a decrease over time (1970-2012). Total liver disease mortality has decreased from over 20 deaths per 100,000 persons (age standardised) in 1970 to 4.5 per 100,000 in 2012. The age-standardised mortality rate was nearly twice as high for males over the period as compared to females.
- **In 2012** the all ages liver disease mortality rate for males was 5.7 per 100,000 compared to 3.4 per 100,000 for women, based on WHO mortality data.[3 49]
- **Liver cancer prevalence rates** above 15 per 100,000 were estimated for Italy by the GBD study in 2016.[2] Compared to other liver diseases, cancer represents one of the largest proportion of deaths.
- **Liver transplants:** Italy has performed the fifth highest number of transplants since 1968 of all 35 focus countries. Viral and alcoholic cirrhosis account for 70% of transplantations.[50]
- **Viral hepatitis** is a major contributor to total liver disease in Italy. The ECDC estimated a 5.9% prevalence of Hepatitis C for the period 2005-2015.[14]
- **Alcohol consumption** in Italy has been decreasing significantly over recent decades.
- **Obesity and liver disease:** The prevalence of obesity in 2013 was approximately 10% for women and 12% for men, which indicates a small overall increase since 2000. Deaths from NAFLD over the same period have fluctuated, although a sharp increase was observed between 2010 and 2013.
- **Liver disease** 40% of PYLL are working years, illustrating that liver disease is a both a large economic and healthcare burden in Italy.

Liver disease mortality in Italy

Liver disease is responsible for 152 years of potential life lost per 100,000 population, of which 62 years or 41% were working years of life lost. This is compared with other chronic diseases such as ischemic heart disease where 35% of PYLL were working life years (Table 1).

Table 1. Potential working years of life lost by selected chronic diseases

Disease	PWYLL (years per 100,000 population)	PWYLL as a proportion of PYLL
Total liver disease	62	41%
Ischemic heart disease	59	35%
Stroke	40	40%
Lung cancer	59	31%

Liver disease mortality by cause of death

Liver cancer is the biggest cause of liver deaths in males and females of all ages, with little change over time. The proportion of deaths accounted for by alcoholic and autoimmune liver disease has remained small and stable over time, whereas the proportion of deaths from viral hepatitis has increased over the last decade.

Figure 54 (females) and Figure 55 (males) show similar patterns in liver deaths by cause, but females have a lower overall death rate from liver disease than males. A slightly greater proportion of deaths amongst males are due to alcohol and cancer, and a slightly greater proportion of deaths amongst females are due to hepatitis and unknown causes.

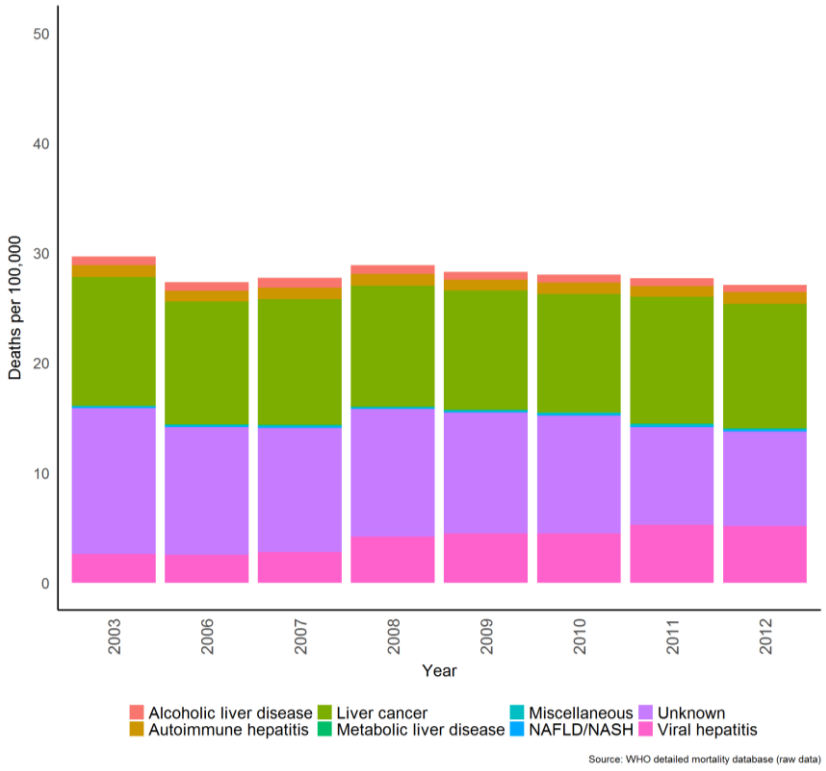


Figure 54. Female age standardised mortality from all liver disease by aetiology over time for Italy

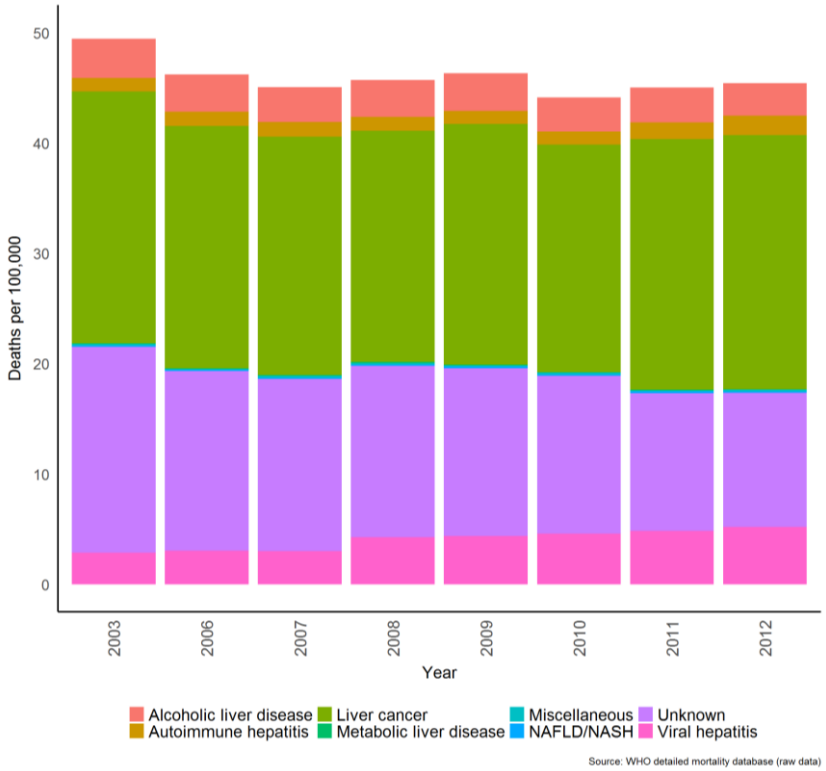


Figure 55. Male age standardised mortality from all liver disease by aetiology over time for Italy

Liver cancer in Italy

In Italy liver cancer is responsible for the largest proportion of liver disease mortality however; there has been a small decrease in liver cancer deaths over time.

Figure 56 and Figure 57 show similar patterns of liver cancer mortality for females and males respectively, but cancer deaths are considerably higher amongst males than females - more than double the rate for some age groups in particular survey years.

Amongst females under 55 years of age, liver cancer mortality has remained stable over time; in age groups older than 55 years, liver cancer mortality has declined slightly, with the exception of the 85+ years age group which has marginally increased. At each time point, the older groups are the most affected, increasing from the age of 55 years, and by a substantial magnitude for each age group upwards; low cancer mortality rates are observed amongst females under 50 years.

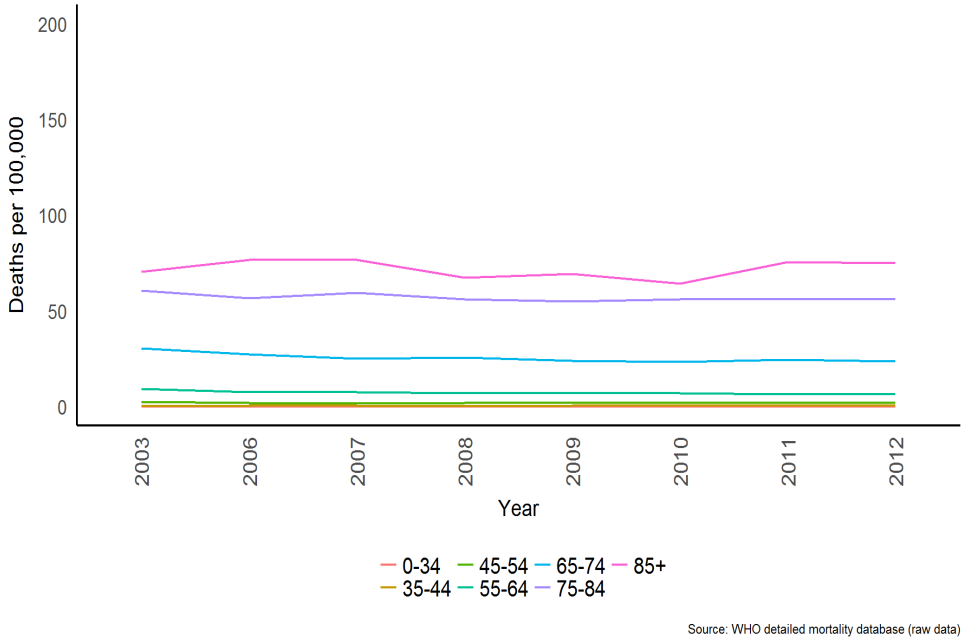


Figure 56: Female mortality from all liver disease by age group for Italy

Amongst males the same age related pattern was observed as for females, with stability in death rates amongst under 55 year age groups over time, and marginal reductions amongst all other age groups except males 85+ years. Again, liver cancer mortality was highest amongst those 55 and older at all time points, with escalating mortality rates for each age group upwards.

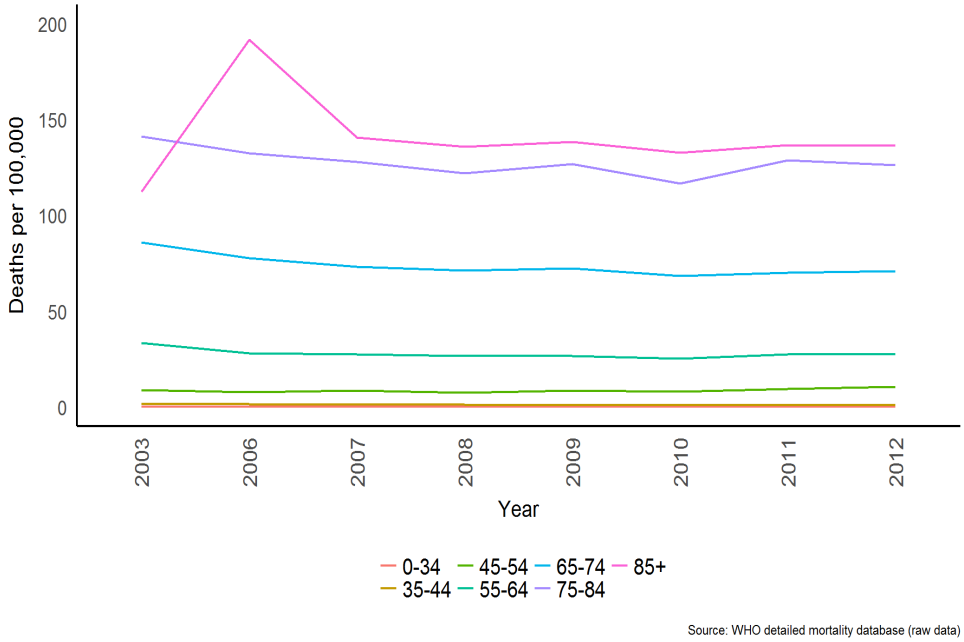


Figure 57: Female mortality from all liver disease by age group for Italy

Alcoholic liver disease in Italy

In Italy from 2003 to 2012 there has been an overall decline in alcoholic liver disease (alcoholic liver disease) deaths. However, as with liver cancer mortality, men have a higher alcoholic liver disease mortality rate, with male rates nearly five times higher than female mortality rates. The overall reduction is mostly accounted for by declines in alcoholic liver disease deaths amongst 50-74 year olds, although this age range still accounts for the largest proportion of alcoholic liver disease deaths at each time point. Alcoholic liver disease deaths begin to decline from 75 years and older; the lowest proportion of alcoholic liver disease deaths are amongst the youngest age groups.

Amongst females (Figure 58), the highest rates of alcoholic liver disease deaths are amongst the 55-74 year age groups, closely followed by 45-54 year olds. The lowest levels of alcoholic liver disease deaths are found amongst the youngest age groups, those under 35 years of age. Alcoholic liver disease deaths have been stable or have reduced slightly in most age groups over time.

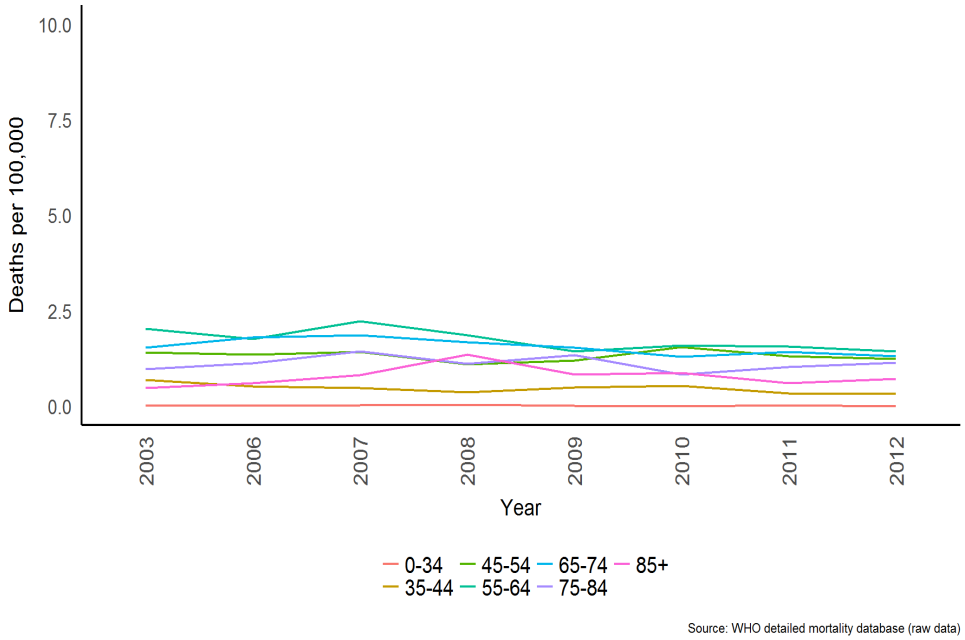


Figure 58. Female mortality from alcoholic liver disease by age in Italy

Males (Figure 59) aged 50 years and older account for the most deaths by alcoholic liver disease. Men in their 40s dominate the middle of the graph, and men under 35 years of age have the lowest alcoholic liver disease deaths. Over time, alcoholic liver disease death trends have remained stable or have reduced slightly amongst most age groups, although there has been a notable reduction amongst the 65-74 year age group. The greatest fluctuations in alcoholic liver disease deaths over time are amongst men 55 years and older.

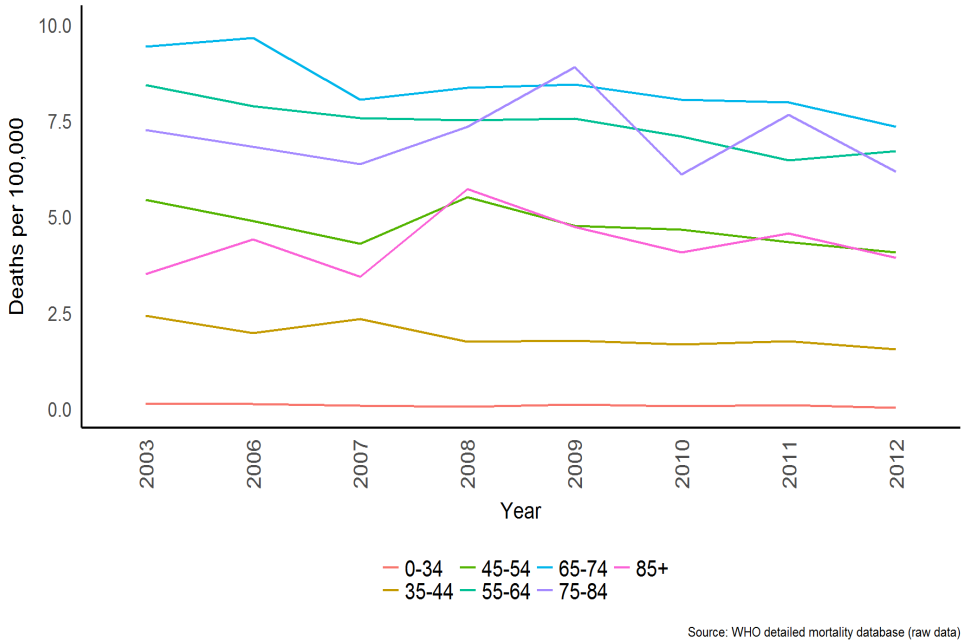


Figure 59. Male mortality from alcoholic liver disease by age in Italy

Figure 60 below shows close mirroring of alcohol consumption (black line) and deaths from chronic liver disease and cirrhosis (blue solid line); both have decreased substantially over time.

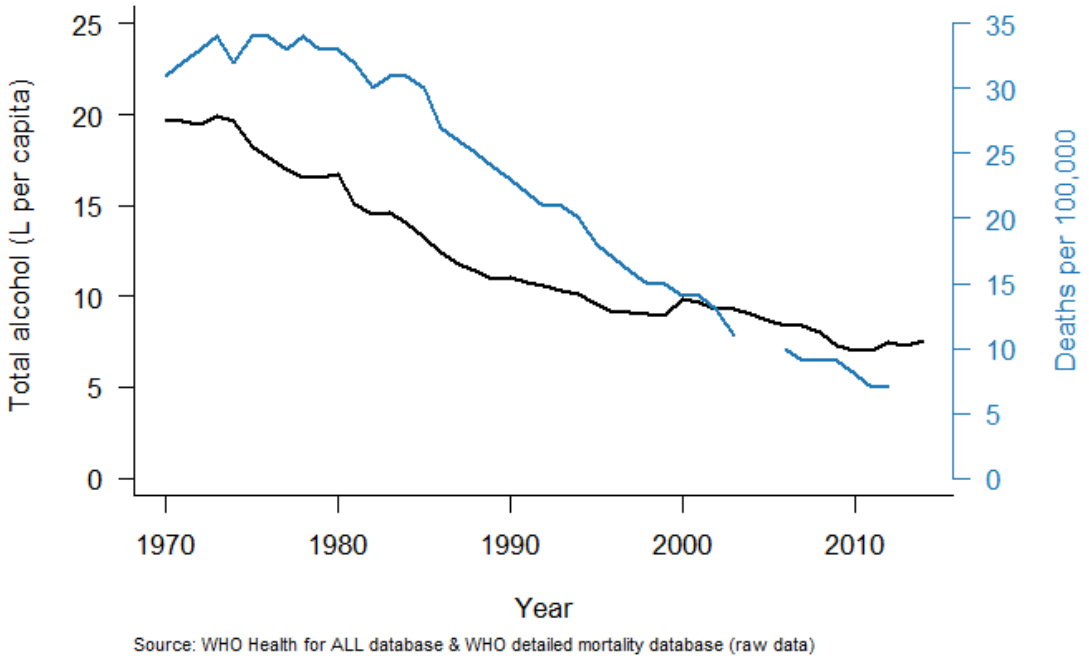


Figure 60. Alcohol consumption (black line) and age-standardised mortality from cirrhosis and chronic liver diseases (blue filled line) and alcoholic liver disease mortality (blue dashed line) in Italy

Alcohol policy environment

The WHO has been compiling key alcohol related policies for the period 2006-2014 (Table 2).[51] The largest decline in alcohol related liver disease deaths was in the period 2010-2012. This coincided with a greater focus on leadership, awareness and commitment related policies, and corresponding evaluations to assess their implementation. For example, regional prevention plans were introduced to address alcohol related harm with a focus on specific 'at risk' groups. A pricing policy also came into effect in 2010, with a change in excise tax laws. In 2012 the minimum age for buying alcohol was increased to 18 years, as part of an alcohol availability policy. Although it is not possible to attribute these policies to the decline in alcohol related liver disease deaths, they may have contributed to this positive finding.

Table 2. Years of active alcohol related policy (2006-2014, WHO data) in Italy

Policy	Years active
Monitoring and surveillance	2010-2014 + 3 annual activities
Leadership, awareness and commitment	2008, 2010-2014
Drink driving policies and counter measures	2006, 2007, 2009, 2010, 2012
Health services' response	2006-2009
Community and workplace action	2006, 2008
Availability of alcohol	2012
Pricing policies	2010

Health services

In 2006, a questionnaire to enable early identification of problem drinkers was introduced into primary care. In 2007, as part of the 'Gaining Health' programme, a primary care strategy to strengthen primary and secondary prevention of alcohol consumption began which included training of primary health care providers and continued through 2012. In 2008-09 the national alcohol and health plan was implemented, with projects focused on prevention, early identification, and workplace interventions.[51]

Socio-demographic changes

The Europe 2020 strategy has assigned employment, education and poverty reduction targets to Italy, for which there are monitoring data available for 2008-2016.[51] During this period, employment rates have remained largely unchanged (and are currently below the 2020 target), whilst education indicators have improved. The poverty indicators indicate little change or worsening in areas such as numbers of people who are severely materially deprived, and those who are at risk of poverty after social transfers. It will be interesting to observe whether these factors change the current downward trend in alcoholic liver disease deaths to 2012, when mortality data for 2013-16 become available.

Non-alcoholic fatty liver disease/non-alcoholic steatohepatitis in Italy

As shown in the main HEPAHEALTH report there is a low death rate from NAFLD/NASH in all years from 2003 to 2012 (less than 4 per 100,000 for all age groups combined). Over

time there is a pattern of initial decline in NAFLD/NASH deaths, followed by an increase back to 2003 levels by 2012. The absolute change in NAFLD/NASH death rates is small, and is mostly accounted for by people 85 years of age and over, who are also the most affected at each time point.

Viral hepatitis mortality in Italy

Over the last nine years Italy has experienced a year-on-year increase in viral hepatitis deaths between 2003 and 2012, during which time the death rate almost doubled. The increase in viral hepatitis deaths is mostly accounted for by people 75 years and older. Death rates from viral hepatitis increase with increasing age. The highest death rates at all time points are amongst people 85+ years of age. Mortality rates for viral hepatitis cannot be broken down by type; however prevalence rates for hepatitis B and C are presented in Figure 63, Figure 64 and Figure 65.

Figure 61 (females) and Figure 62 (males) show similar death rates for equivalent age groups. There is slightly less variability in death rates over time amongst women less than 60 years of age (consistently <5 deaths/100,000) compared to male counterparts. There have been dramatic increases in viral hepatitis deaths for the two oldest age groups amongst males and females.

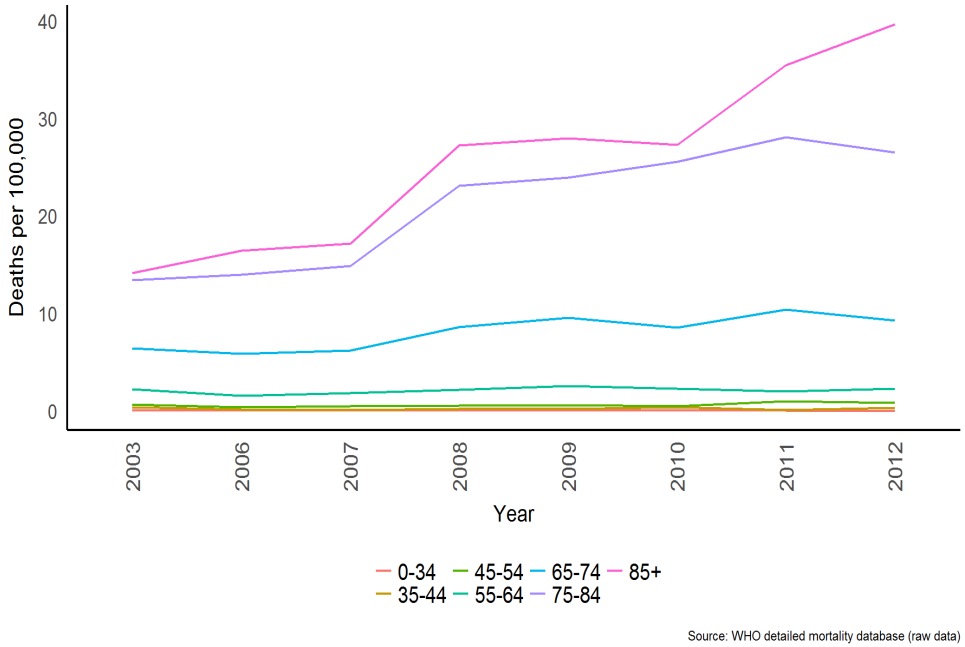


Figure 61. Female mortality from viral hepatitis by age in Italy

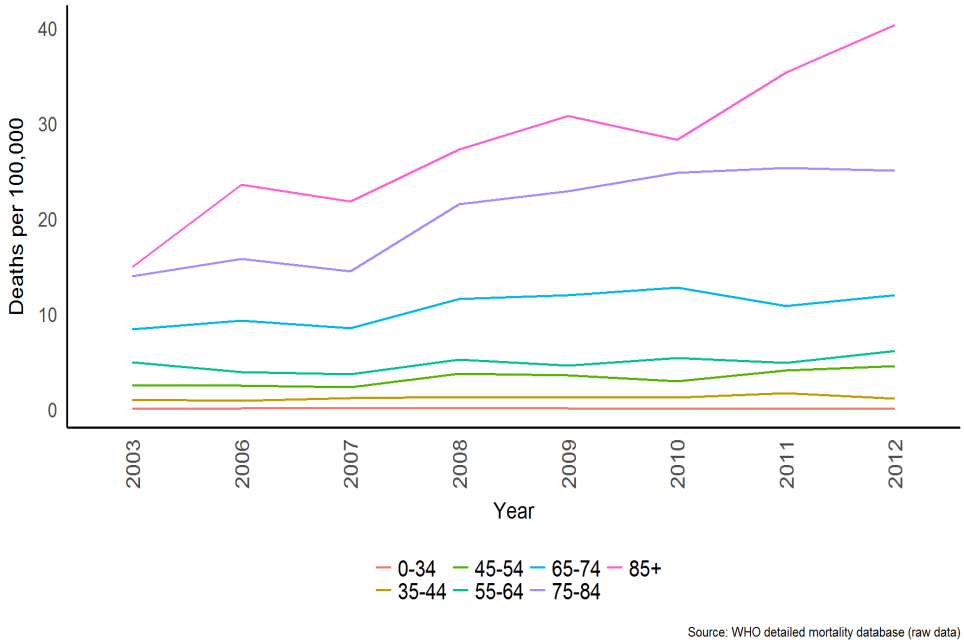


Figure 62. Male mortality from viral hepatitis mortality by age in Italy

Viral hepatitis prevalence in Italy

Hepatitis B

The prevalence of hepatitis B in Italy has fluctuated over time and since the early 2000s has been steadily decreasing. However the latest data point shows that the rate per 100,000 has risen for the first time in 10 years. In 2011, men have higher rates of hepatitis B than women, 1647 per 100,000 compared to 1098 per 100,000, respectively.

Figure 63 shows the prevalence of hepatitis B for women over 40 years of age over time. The graph shows that hepatitis B has been most prevalent amongst the older age groups with those aged 70-79 years accounting for the most cases from 1996 to 2008 after which those aged 55-70 years have the highest number of cases.

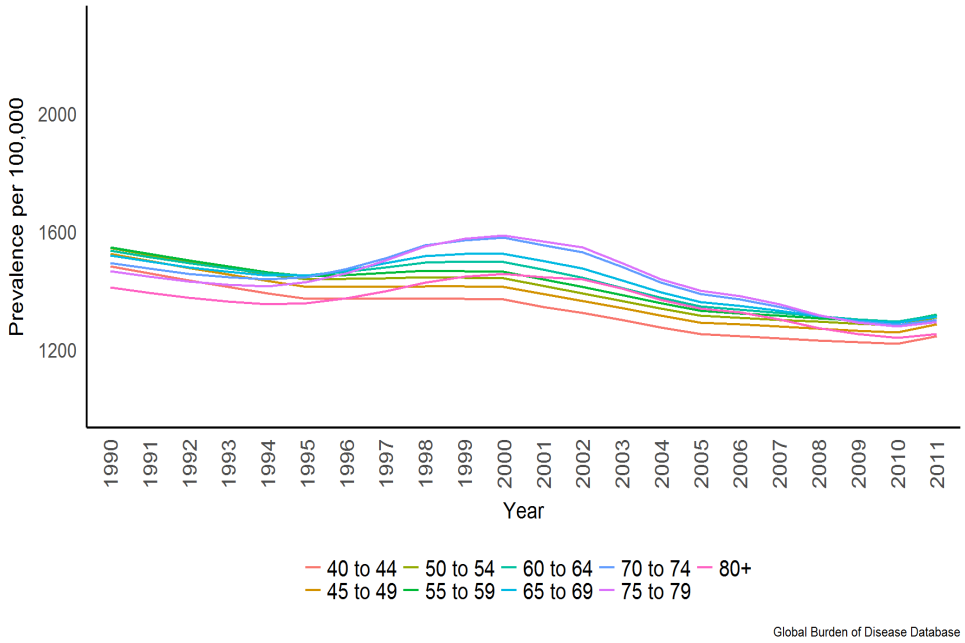


Figure 63. Female hepatitis B prevalence for those aged 40 years and over in Italy – modelled data

Hepatitis B is more prevalent in men than women although the trend over time follows a broadly similar pattern. Hepatitis B is most prevalent in middle to older age groups: since 2005 those aged 45-65 years have had the highest prevalence (Figure 64). Unlike women, men have seen a moderate stabilisation of Hepatitis B prevalence rates since 2005; however rates remain higher among men compared to women.

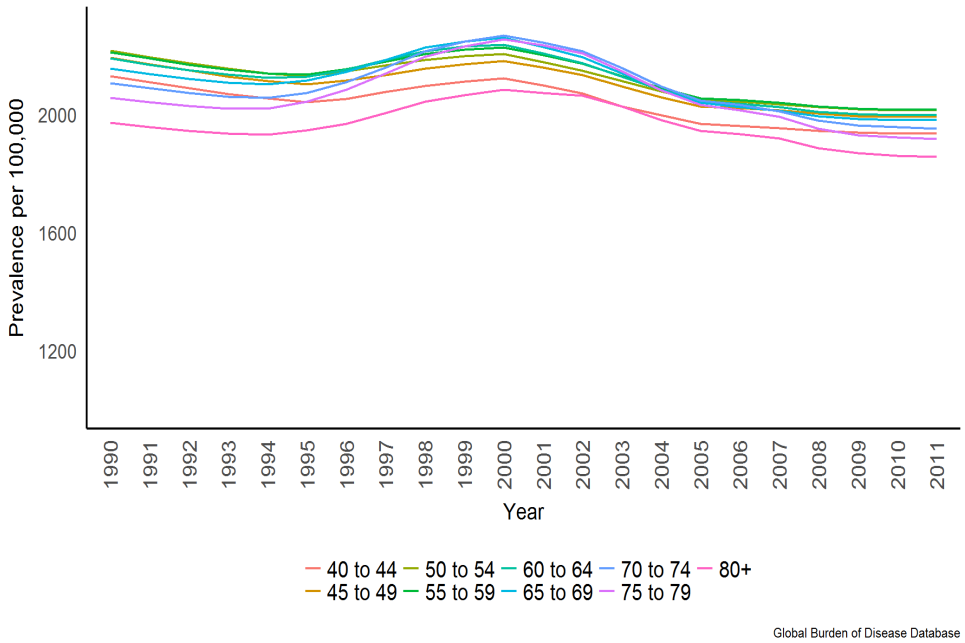


Figure 64. Male Hepatitis B prevalence for those aged 40 years and over in Italy – modelled data

Hepatitis C

Hepatitis C prevalence rates in Italy have been relatively stable over time across all age groups (Figure 65). In the last few years there has been a slow decline in prevalence for all age groups. Hepatitis C is predominately a disease of older people, with those aged above 70 years having over 4000 hepatitis C cases per 100,000 people. Rates of hepatitis C are broadly similar for men and women.

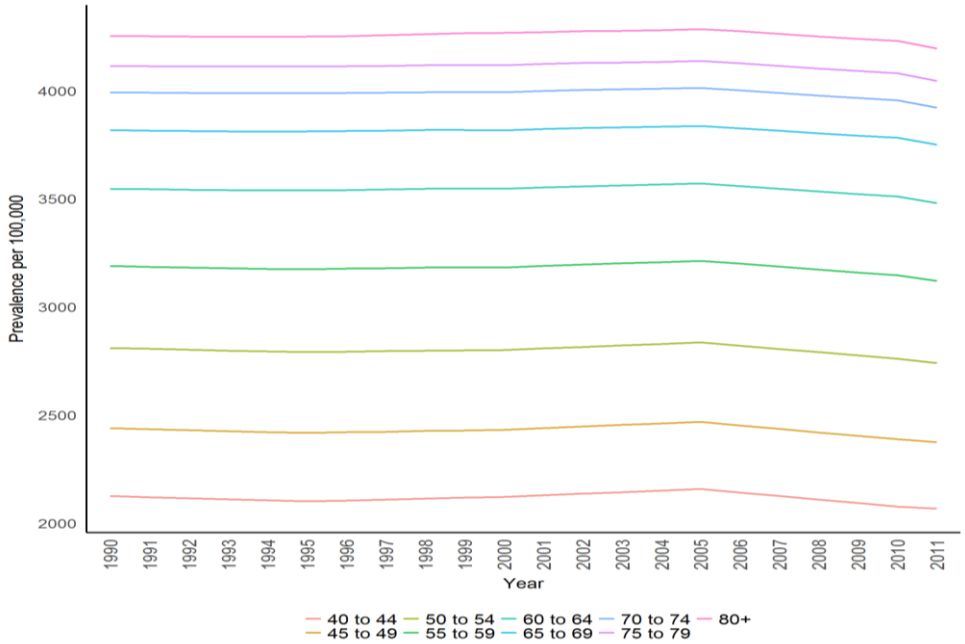


Figure 65. Hepatitis C prevalence for males and females aged 40 years and over in Italy – modelled data

Hepatitis policy environment

Injection drug use is a major risk factor for hepatitis C in Italy, and prevalence is far higher amongst PWIDs than other groups. A 2014 review found that there was no national plan or strategy, or national treatment guidelines for hepatitis C treatment that included PWIDs. Although national plans have been prepared, as of 2014 they had not yet been approved, and clinicians are obliged to follow regional guidelines which vary. This could result in regional disparities in who is eligible for treatment with new, and expensive direct acting antivirals.[52]

A 2011 global policy report identified that Italy was implementing hepatitis prevention strategies with specific populations (e.g. health care workers) but that there was no national plan focused exclusively on the prevention of viral hepatitis.[53] The lack of national coordination is concerning given the rising rate of viral hepatitis deaths.

Health services

The hepatitis B immunisation is mandatory for children <12 months, and is given at birth if the child is born to a woman with known positive status.[54] A 2011 report indicated that Italy had not set a goal to eliminate hepatitis B from the population.[53] As of 2014, six of the 'most

severe' groups of patients were given free access to hepatitis C treatment free of charge amounting to €850 million in 2013-16. Since highly effective hepatitis C treatment has become available, the Health Ministry has begun setting out a pharmaceutical plan to eradicate hepatitis C virus infection within six to eight years.[55]

Conclusion

Liver disease mortality has declined slightly over the last few decades in Italy. The highest proportion of deaths are accounted for by liver cancer, although there are important knowledge gaps given that the second most common cause of liver disease mortality is classed as unknown. Improved data recording and reporting could change the understanding of liver disease in Italy dramatically.

While there is a relatively low burden of alcohol related liver disease and mortality in Italy, men are significantly more affected than women. Alcohol consumption has halved, and alcohol related mortality has decreased from more than 30 deaths per 100,000 to less than 10 deaths per 100,000 since 1970. Recent declines in alcoholic liver disease mortality have coincided with policies reflecting strong leadership and commitment to preventing alcohol related harm, as well as those affecting pricing and availability of alcohol.

Obesity, particularly amongst children, is increasing in Italy. Although deaths from NAFLD/NASH are currently low, unless obesity is curbed the NAFLD/NASH death rate could accelerate in future generations. A greater emphasis on obesity policies, and a coordinated strategy at national level could be critical in curbing the obesity epidemic.

Viral hepatitis is one of the greatest contributors to liver disease mortality in Italy, and it is a common underlying cause of liver cancer. Deaths attributed to viral hepatitis are increasing year-on-year. The government has set ambitious targets to eradicate hepatitis C virus infection within six to eight years with the introduction of effective treatment, however, it will be important for PWIDs to be included in national plans if this target is to be realised.

Case study: Liver disease and risk factor data in Finland

Summary of overall findings

- **Historic trends in liver disease mortality** indicate an increase in mortality (1996-2014). Total liver disease mortality has decreased from 2.4 deaths per 100,000 persons (age standardised) in 1996 to 4.0 per 100,000 in 2014. Males are the most affected by liver disease, with the mortality rate 1.7 times higher than females.
- **In 2014** the all ages liver disease mortality rate for males was 5.7 per 100,000 compared to 2.4 per 100,000 for women, based on WHO mortality data.[3 49]
- **A liver cancer prevalence rate** of 8.5 cases per 100,000 was estimated for Finland by the GBD study in 2015.[2] Compared to other liver diseases, cancer represents the second largest proportion of deaths (second to alcoholic liver disease).
- **Liver transplants** are rare in Finland, with relatively fewer numbers of transplants since 1968 compared to other Northern and Western European countries, partly because of its smaller population. In general, viral hepatitis and alcoholic cirrhosis account for 70% of transplantations.
- **Viral hepatitis** is not a major contributor to total liver disease deaths in Finland. However the burden of viral hepatitis is still large, with the ECDC estimating that chronic hepatitis B affects approximately 7 per 100,000 in 2015.[14] Injection drug use was the most commonly reported route of transmission for viral hepatitis (80%).
- **Alcohol consumption and liver disease deaths** are increasing**.** Finland has observed a significant increase in annual alcohol consumption since 1970. Liver disease deaths related to alcohol represents the largest proportion of deaths in Finland, and has increased since the mid-1990s.
- **The prevalence of obesity** in 2014 was approximately 15-16%, which indicates an overall increase since 2000. Deaths from NAFLD/NASH over the same period have remained low in Finland, against a backdrop of an increasing trend in Northern countries.

Liver disease mortality in Finland

In Finland, there is an estimated 279 years of potential life lost per 100,000 population as a result of liver disease. In Finland, PWYLL per 100,000 population accounts for nearly half of the PYLL per 100,000 with 45% of years of life lost coming from people of working age. Stroke, shows that 38% of PYLL are from those of working age, while diseases such as heart disease and lung cancer are below 30% (Table 3). The increased number of PWYLL demonstrates the economic burden that liver disease is costing Finland, this has been reiterated in the qualitative interviews where specialists have been very concerned by in the increase in mortality and morbidity among younger age groups (45 years and over).

Table 3: Potential working years of life lost by various chronic diseases in Finland

Disease	PWYLL (years per 100,000 population)	PWYLL as a proportion of PYLL
Total liver disease	125	45%
Ischemic heart disease	78	29%
Stroke	46	38%
Lung cancer	35	27%

Liver disease mortality by cause of death

Alcoholic liver disease is the biggest cause of deaths related to liver disease in males and females of all ages. Mortality from alcoholic liver disease has increased substantially between 1996 and 2014. The next most common cause of liver disease mortality is from liver cancer and the proportion of deaths by liver cancer has increased slightly over time. The proportion of deaths accounted for by autoimmune liver disease and viral hepatitis has remained small and stable over time. Compared to other focus countries (e.g. Italy) the proportion of deaths from unknown causes is very low, reflecting the strengths of Finland's data recording systems.

Figure 66 (females) and Figure 67 (males) show slightly different patterns in liver disease mortality by cause. Females have a lower overall liver disease mortality rate than males (approximately 18 per 100,000 versus 45 per 100,000 in 2014). For both sexes, alcoholic liver disease is the biggest cause of liver disease mortality, which has increased over time - gradually for females, and sharply for males. Amongst females, liver cancer accounts for almost as many deaths as alcoholic liver disease. Compared to males, there are a greater proportion of deaths due to autoimmune liver disease, and a greater proportion of liver deaths that have an unknown cause. Amongst males, alcoholic liver disease has accounted for about two-thirds of all liver deaths since 2004; deaths due to liver cancer are the second most common cause of liver disease mortality, and have increased marginally over time.

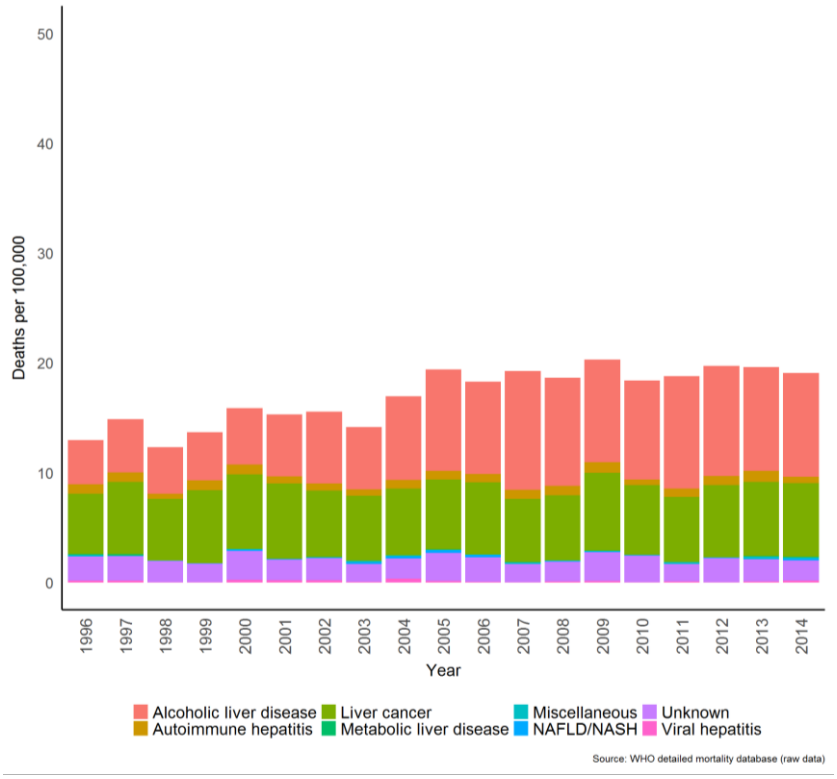


Figure 66. Female age standardised mortality from all liver disease by aetiology over time in Finland

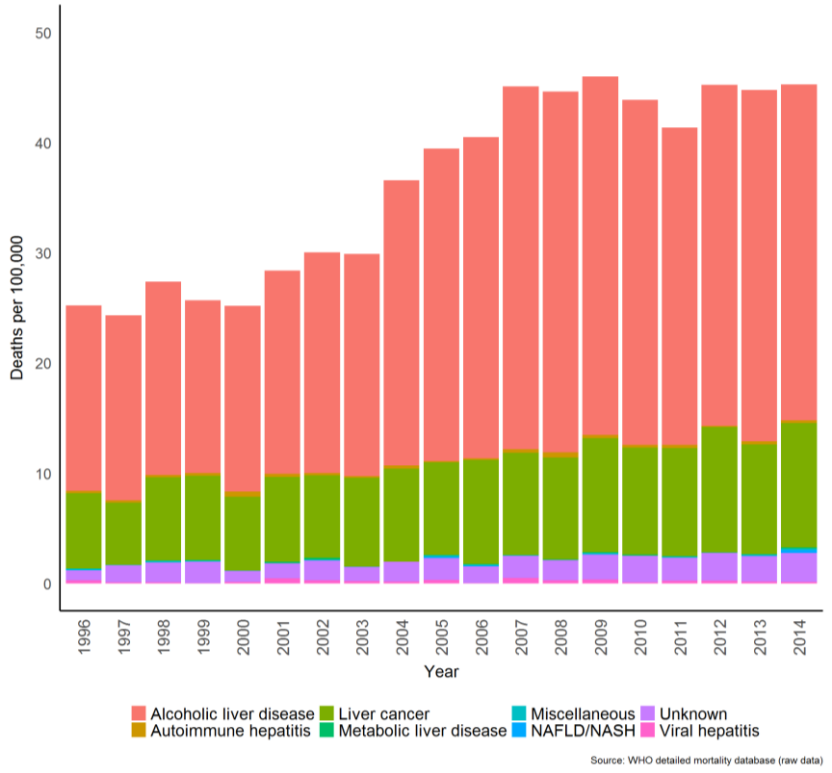


Figure 67. Male age standardised mortality from all liver disease by aetiology over time in Finland

Alcoholic liver disease in Finland

Finland has seen a substantial increase in liver disease deaths related to alcoholic liver disease, starting in the early 2000s. The mortality rate over the 18 year time period has doubled, from 10.3 deaths per 100,000 in 1996 to 19.8 deaths per 100,000 in 2014. For much of the time period and for most age groups males have over three times the mortality rate compared to women. Those under the age of 35 years and over the age of 85 years have had relatively stable rates of alcoholic liver disease deaths; however every age group has seen an increases in alcoholic liver disease mortality rates.

Alcoholic liver disease deaths are generally higher amongst males than females at all ages (see Figure 68 and Figure 69). Amongst females (Figure 68), the highest rates of alcoholic liver disease deaths are those in the 55-74 years age group. The lowest levels of alcoholic liver disease deaths are found amongst the youngest age groups. Alcoholic liver disease deaths have fluctuated considerably in people 50 years and over, with sharp increases observed amongst the 55-74 year olds between 1996 and 2014. Female all ages mortality rates have more than doubled over the time period, from 4.0 per 100,000 in 1996 to 9.4 per 100,000 in 2014.

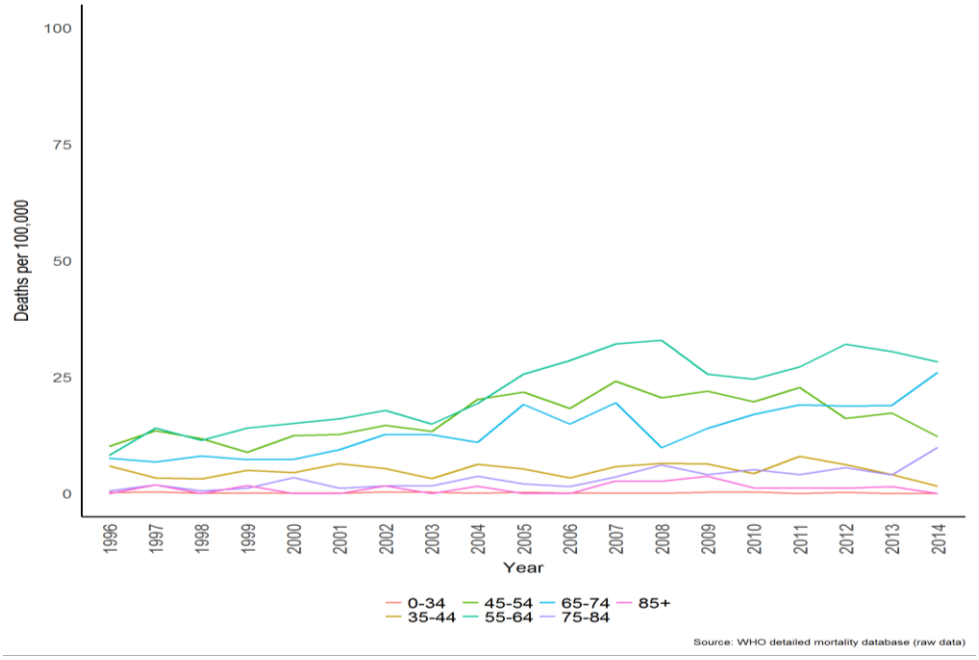


Figure 68. Female mortality from alcoholic liver disease by age in Finland

Alcoholic liver disease mortality rates are three times as high for males than for females (all ages, 30.5 per 100,000 vs 9.4 per 100,000 respectively). Male mortality rates have almost doubled over this time period and those aged 50-74 years are the most affected by alcoholic liver disease deaths (Figure 69). Male alcoholic liver disease death rates are higher from a younger age with those aged 35-44 years showing much higher rates than females. However, both sexes at this age show a decline in recent years. Males, 30 years and under, have the lowest and most stable rates of alcoholic liver disease deaths over time. Alcoholic liver disease deaths amongst males 50-74 years have increased overall, although they appear to have peaked in 2007-2008 and have begun to decline to 2014; the greatest

fluctuations in alcoholic liver disease deaths over time are also seen amongst this age range.

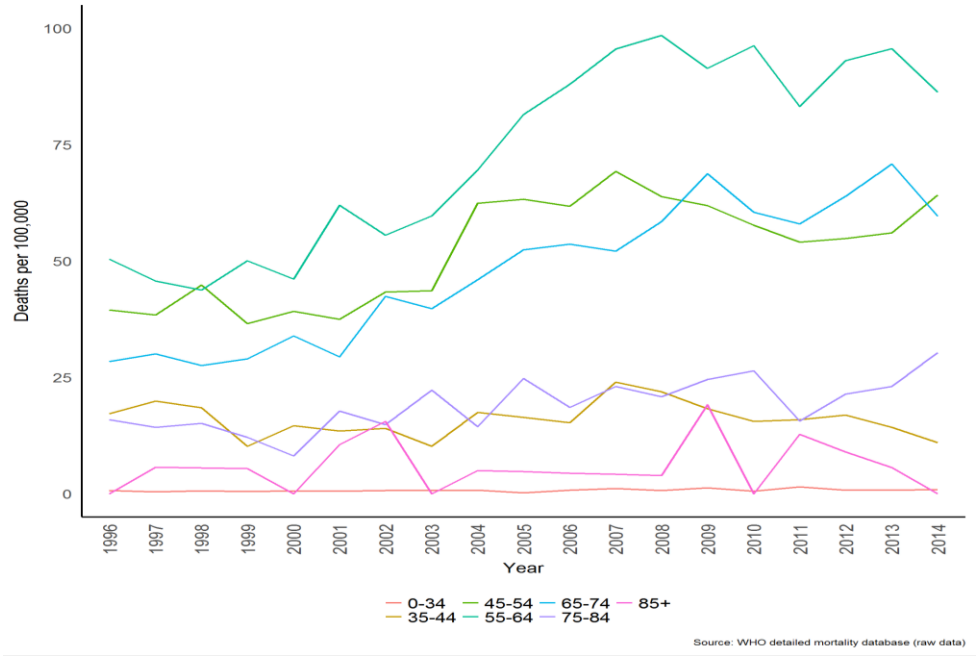


Figure 69. Male mortality from alcoholic liver disease by age in Finland

Figure 70 below shows that alcohol consumption has increased marginally over time, but that deaths from liver disease and cirrhosis, and deaths from alcoholic liver disease, have increased substantially. There is approximate mirroring of alcohol consumption (black line) and deaths from chronic liver disease and cirrhosis (blue solid line) from 1970 to 1985, at which point alcohol consumption levels off, but cirrhosis and total chronic liver disease deaths increase sharply to 2010; a similar pattern in observed for alcoholic liver disease (blue dotted line).

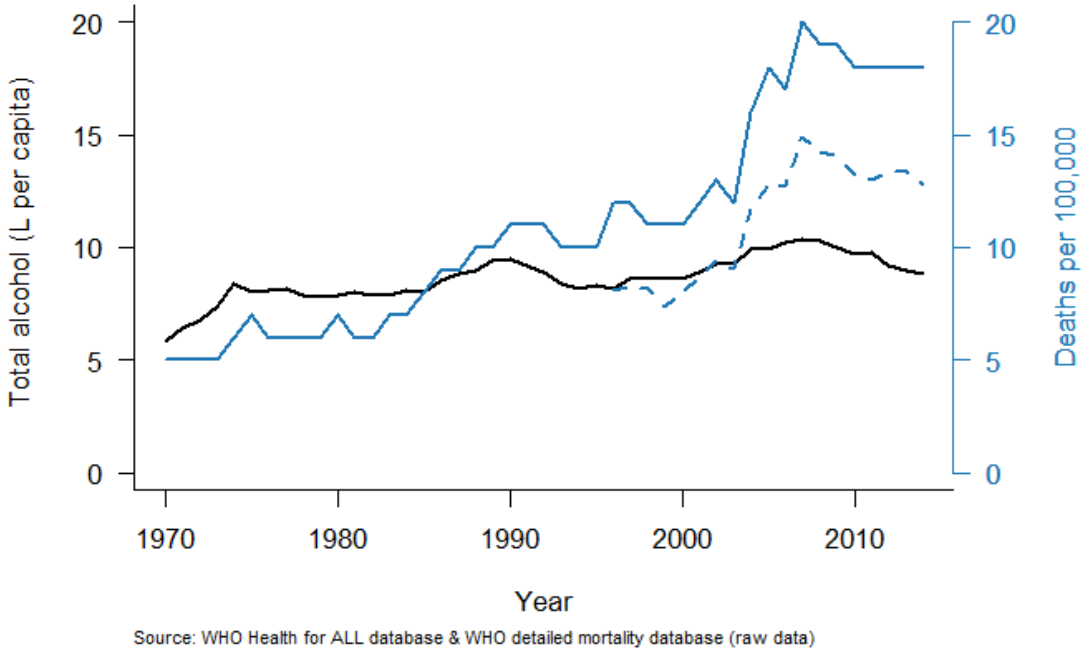


Figure 70: Alcohol consumption (black line) and age-standardised mortality from cirrhosis and chronic liver diseases (blue filled line) and alcoholic liver disease mortality (blue dashed line) in Finland

Alcohol policy environment

In recent decades, there has been a gradual dismembering of the 'three pillars' of Nordic alcohol policy: 1) restrictions in private/for profit alcohol business, 2) restricted physical alcohol availability (e.g. opening hours), and 3) restricted economic alcohol availability (e.g. taxation).[56] The WHO has been compiling key alcohol related policies for the period 2006-2014 (Table 4).[51] The largest spike in alcohol related liver disease deaths occurred in the period 2005-2007; the curve starts to flatten from 2010, which coincides with new policy activity. The spike coincided with the removal of quotas for travellers' alcohol imports within the EU in 2004, enabling large quantities of alcohol to be brought in from countries where alcohol is cheaper – Estonia in particular – as well as lowering of the excise tax on alcohol. There was a subsequent increase in excise tax in 2008 and 2009.[56]

Table 4: Years of active alcohol related policy (2006-2014, WHO data) in Finland

Policy	Years active
Monitoring and surveillance	2010, 2011, 2013
Leadership, awareness and commitment	2007, 2011, 2014, 2015
Drink driving policies and counter measures	2010, 2012
Health services' response	2011, 2013, 2015
Community and workplace action	2014, 2015
Availability of alcohol	2013
Pricing policies	2014, 2015

Health services

A primary care register to enable and record screening and treatment interventions for alcohol use disorders was launched in 2011. The same year, the government ordered 'prevention counselling, early identification and treatment of alcohol and drug problems' to take place at maternal and child clinics, and in school settings. In 2013, handbooks used in maternity and child clinics were updated to include a section on parents' drinking habits. In 2015 a new 'Act on organizing alcohol, tobacco, drugs and gambling prevention' was implemented, which includes a new action plan implemented by the National Institute of Health and Welfare to promote health and wellbeing. Prior to 2011 there were no recorded alcohol policies involving health service response.[51]

Socio-demographic changes

The Europe 2020 strategy has assigned employment, education and poverty reduction targets to Finland, for which there are monitoring data available for 2008-2016.[57] During this period, employment rates have remained largely unchanged, but close to the 2020 target, whilst education indicators have already been met or are close to being met. The poverty indicators indicate improvement in most indicators but still some distance from the EU2020 target; there has been an increase in the number of people who are at risk of poverty after social transfers. Population changes according to the Finnish census are minimal, more than 95% of the population are native to Finland, with just under three percent originating from other European countries, and just over 1% from Asia.[58]

Social attitudes

Opinion polls conducted between 2003 and 2013 show a positive correlation between alcohol consumption and people's preference to bring in more restrictive alcohol policies. This is attributed to greater awareness amongst the general public about the harmful effects of alcohol following the introduction of more liberal alcohol policies in 2004.[59]

Liver cancer in Finland

In Finland there is an increasing risk of death from liver cancer with increasing age. There has been a moderate increase in liver cancer deaths between 1996 and 2014, although the cancer deaths have fluctuated in the intervening years.

Figure 71 (females) and Figure 72 (males) show similar patterns of liver cancer mortality over time for females and males, but cancer deaths are considerably greater amongst males than females – almost double the rate for some age groups in particular survey years. Amongst females under 75 years of age, liver cancer mortality has remained stable over time. In age groups older than 75 years, liver cancer mortality has fluctuated substantially between 1996 and 2014, although the overall change for each age group is marginal. At each time point, the older groups are the worst affected, increasing from the age of 65 years, and by a substantial magnitude for each age group upwards. Low levels of cancer mortality are observed amongst females under 55 years. Amongst males there was overall stability in death rates in those aged under 75 years between 1996 and 2014, with some fluctuations in the intervening years. The oldest age groups showed marginal increases in liver cancer

mortality rates over time. A similar age related pattern in liver cancer mortality was observed as among females, with deaths noticeably increasing from the age of 55 years, and with escalating mortality rates for each successive age group.

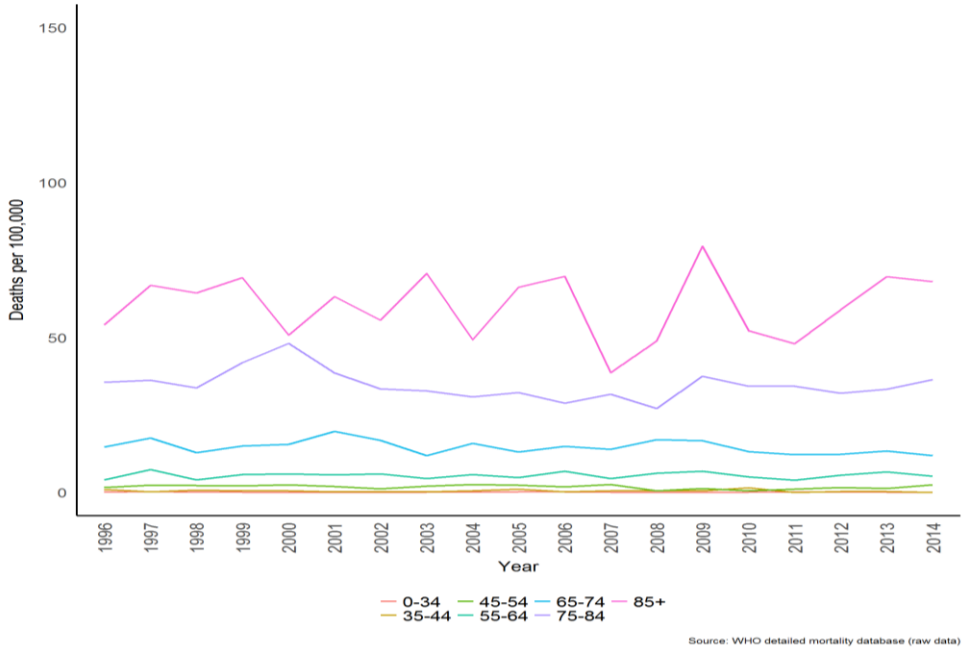


Figure 71.Female mortality from liver cancer by age in Finland

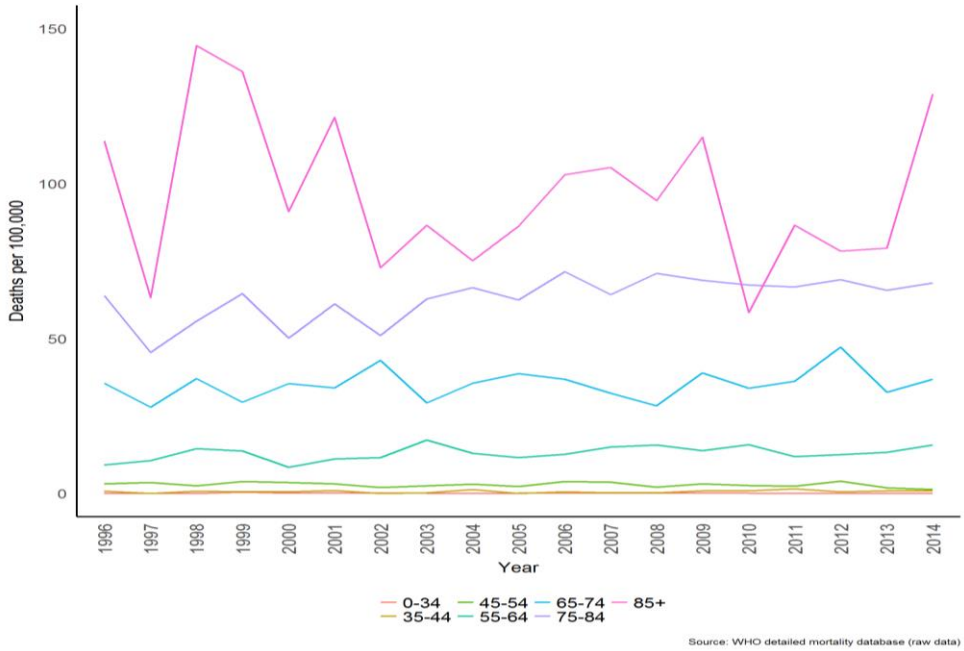


Figure 72. Male mortality from liver cancer by age in Finland

Non-alcoholic fatty liver disease/non-alcoholic steatohepatitis in Finland

Finland has a low death rate from NAFLD/NASH in all years from 1996 to 2014 (approximately 4.5 per 100,000 for all age groups combined in 2014). Over time there has been an initial increase in NAFLD/NASH deaths peaking in 2005/6, followed by a sharp decrease to 2013, and another sharp increase in 2014. The absolute change in NAFLD/NASH death rates is small. NAFLD/NASH deaths are mostly accounted for by people over 65 years of age, although this is not true for every survey year, and results could be affected by small population numbers per age group where NAFLD/NASH is the underlying cause of death.

NAFLD/NASH death rates are similar between males and females for all age groups with the oldest age groups tending to be the most affected. These age groups also show the greatest fluctuations in death rates over time, although the rates are low in absolute terms.

Obesity prevalence and liver cancer mortality in Finland has slightly increased over the last 15 years. Amongst females the prevalence of obesity has risen by about five percentage points between 2000 and 2015 (estimated at 15% for 2015). Over the same time frame deaths from cancer have increased marginally, and by a lesser degree than obesity, estimated at around 7 per 100,000 in 2015. Amongst males obesity has risen by a similar magnitude as for females, beginning at a slightly higher prevalence, and peaking at approximately 17% in 2015. Deaths from liver cancer amongst males have risen proportionally to the rise in obesity, estimated at 11 per 100,000 in 2015.

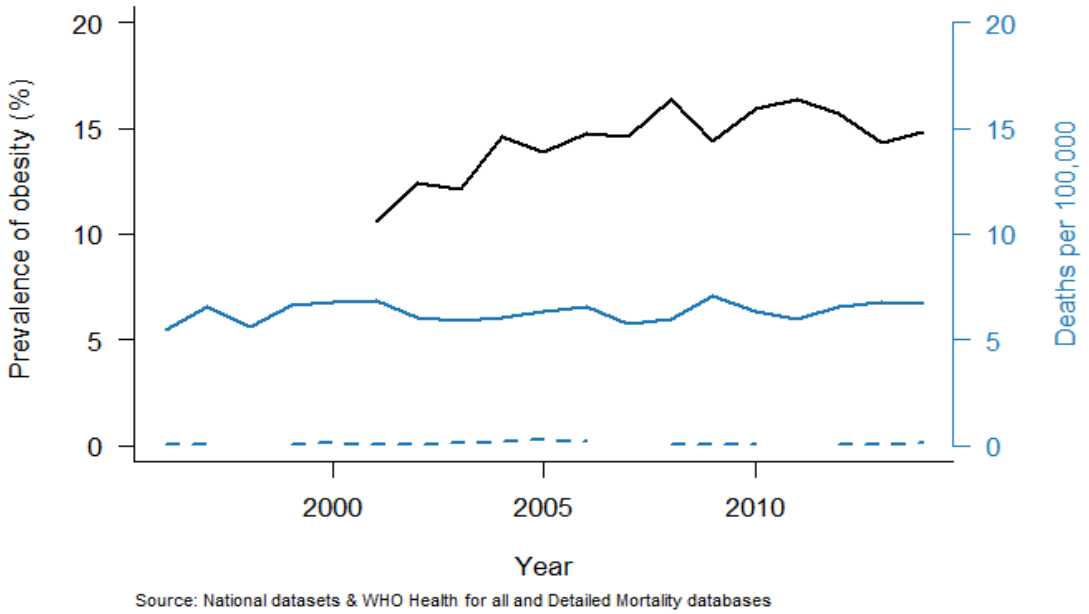


Figure 73. Female obesity prevalence (black line) and age-standardised mortality from liver cancer (coloured line) and NAFLD (coloured dashed line) in Finland (all ages)

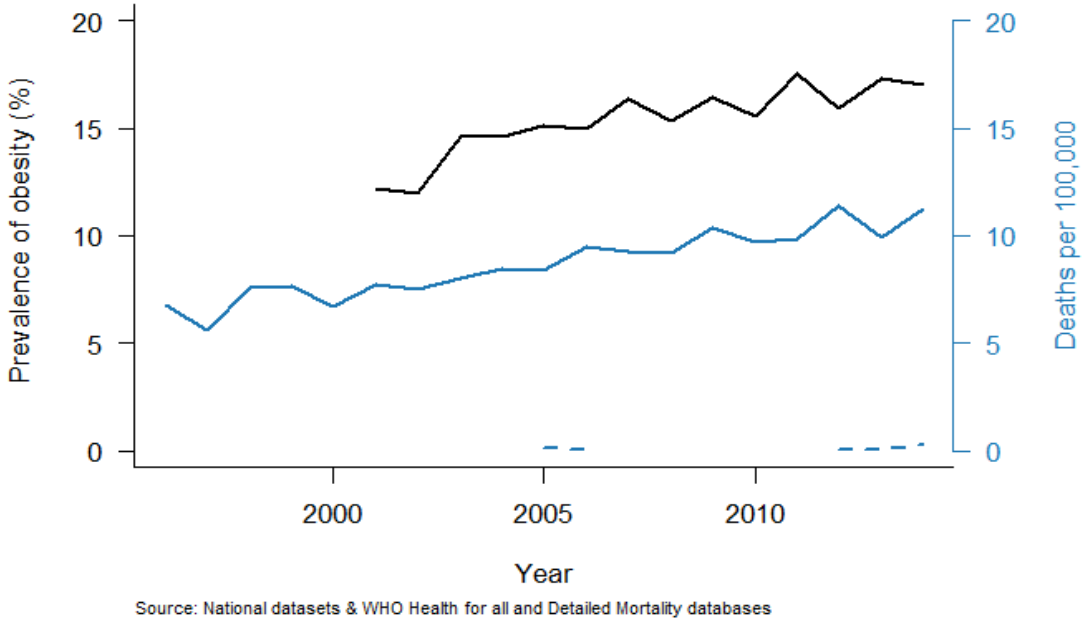


Figure 74. Male obesity prevalence (black line) and age-standardised mortality from liver cancer (coloured line) and NAFLD (coloured dashed line) in Finland (all ages)

Obesity policy environment

Finland is nearing the end of its current National Obesity Programme (2012–2018). It aims to achieve a downward trend in the obesity in order to improve health and welfare and to maintain the population's functional and work ability through encouraging multi-sectoral working across a range of settings and with a number of partners and key actors.[60] In some municipalities, there has been recognition of the need to address childhood obesity. A recent case study in the City of Seinäjoki demonstrated substantial reductions in childhood obesity as a result of implementing a multi-sectoral programme called 'overcoming obesity'. Underpinning the programme was the principle to incorporate 'Health in All Policies' as part of the Health Care Act.[61] For NAFLD/NASH deaths to remain low in Finland adult obesity will also need to be addressed, as obesity trends are currently on the increase.

Viral Hepatitis in Finland

Between 1996 and 2014 there has been an overall decrease in viral hepatitis deaths in Finland. Fluctuations are apparent in the intervening years, although the death rate and its fluctuations are low in absolute terms. Up to 2009, most viral hepatitis deaths were accounted for by people 70 years and over, whereas in the most recent year there is a more even distribution across age groups. It is not possible to disentangle the different types of hepatitis that are accounting for these deaths; however prevalence by type of hepatitis can be explored.

The prevalence of hepatitis B has declined from 1990 to 2016, with age standardised rates for males dropping from 1446 per 100,000 in 1990 to 1285 per 100,000 in 2016. Females reduced by a similar amount, 946 per 100,000 to 826 per 100,000 between 1990 and 2016,

respectively. Hepatitis B prevalence is higher amongst the middle aged with people aged 50-60 years having the highest rates per 100,000 population (Figure 75). Hepatitis C prevalence has remained steady across this time period for both males and females at rates of approximately 1200 per 100,000 for females and 1380 per 100,000 for males.

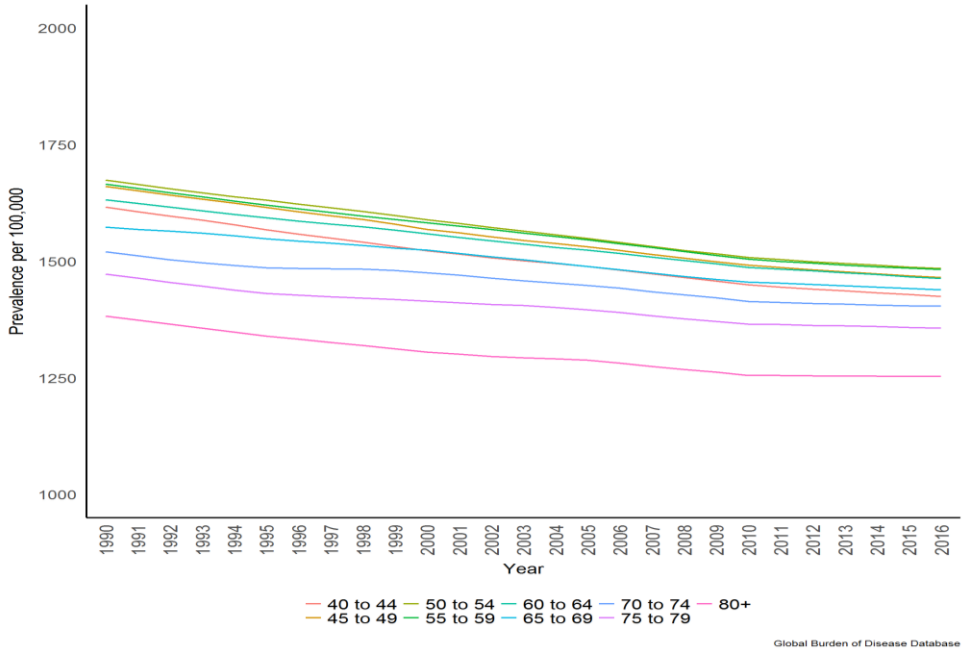


Figure 75. Males and females hepatitis B prevalence for those aged 40 years and over in Finland– modelled data

Viral hepatitis policy environment

Whilst there is a relatively low burden of viral hepatitis and associated deaths in Finland, the lack of policies around the prevention and treatment of hepatitis C mean the country could be unprepared should there be an increase. According to a 2014 review, Finland was in the process of developing a national hepatitis C treatment strategy and action plan. However, it was also noted that PWID are excluded from publically funded treatment.[62] In Finland, 80% of viral hepatitis infections are acquired through injection drug use and given the high costs of direct-acting antivirals, those in most need of treatment are unlikely to receive it. The Hepatitis B vaccine is not offered to children or adolescents in Finland, but it is offered to people deemed to be 'at risk'.[63]

Conclusion

Liver disease mortality in Finland is dominated by the increasing morbidity and mortality from alcoholic liver disease. Alcoholic liver disease is by far the most common cause of liver disease mortality. Death rates are unacceptably high for men and women, and have dramatically increased over the last three decades. There are signs that the death rate from alcoholic liver disease is beginning to plateau, which may be partly due to the introduction of more restrictive policies, and changes in social attitudes.

Mortality from NAFLD/NASH and liver cancer are low in Finland, but have the potential to increase if adult and childhood obesity increases from current levels. There have been successes in some municipalities in terms of reducing childhood obesity by adopting a 'health in all policies' approach.

The burden of viral hepatitis and associated deaths is currently low in Finland. However, the country is lacking in key policies and action plans related to prevention and treatment. The exclusion of people who use injection drugs from publically funded effective hepatitis C treatment means that there may not be any meaningful reduction of current levels, and that those most in need of treatment will not be able to access it for financial reasons.

PART 3: POLICIES AND PUBLIC HEALTH INTERVENTIONS TO REDUCE THE RISK FACTORS FOR LIVER DISEASE

The aim of this third section was to summarise the recent evidence on the public health interventions that impact on the main modifiable risk factors for liver disease. Interventions included are those to prevent and reduce 1) the harmful use of alcohol, 2) the prevalence of obesity and diabetes, and 3) the prevalence of hepatitis B and C. In addition, interventions to screen for and identify all liver diseases (including those with a genetic aetiology that may not be prevented through behaviour modification) are outlined here. Upstream interventions on the modifiable risk factors for liver disease (alcohol consumption, excess weight, diabetes type 2 and hepatitis B and C infection) were the focus for this report. A review of treatment practices and recommendations was beyond the scope of this report, except in the case of hepatitis B and C infection, as treatment of a communicable disease has the potential to reduce the risk of infection in the population and so can be considered a form of upstream, population-level prevention. When identified, evidence on interventions which had a direct impact on liver disease epidemiology were included, but the majority of reviews focussed on reducing the risk factors themselves, without further information on downstream effects on liver disease mortality and morbidity.

Methods

The approach adopted was to conduct a 'review of reviews'. A search of the peer-reviewed and grey literature was conducted to identify potential studies and reports which reviewed interventions to reduce the upstream, behavioural and modifiable risk factors for liver disease. When no review or summary report on an intervention was identified, information from individual studies was extracted.

Snowballing of the identified resources through contacts was undertaken to find additional relevant sources for review.

Title and abstract screening of search results, followed by single-reviewer full-text review for eligibility was undertaken. Included reports were grouped according to the risk factor targeted, and separate narrative reviews were written up on the sets of interventions. In cases where many relevant reviews, modelling studies or individual studies were deemed relevant, detailed summaries of the study methods and findings were collected into tables.

Interventions to reduce alcohol consumption and harm from alcohol

Several organisations and individuals have reviewed the available evidence on effective alcohol policies. These include the European Alcohol Policy Alliance's review, taking into account the policies' effectiveness, the strength of the evidence base, the extent to which they have been tested cross-culturally, and the relative expense of their implementation.[64] The World Health Organization's report 'From Burden to "Best Buys": Reducing the

Economic Impact of Non-Communicable Diseases in Low- and Middle-Income Countries' lists three best buy interventions to reduce harm from alcohol consumption.[65] The OECD carried out an extensive review of the economics and public health policy to tackle harmful use of alcohol.[32]

Across all of these reports, the public health approaches to reducing harm from alcohol consumption can broadly be categorised into population-level and individual-level policies.

Population level policies include fiscal policies, which include taxation and price regulation; policies regulating the marketing of alcohol, and policies managing the drink environment and availability of alcohol. Individual-level interventions include screening for alcohol use and abuse and brief interventions for alcohol consumption reduction.

In the peer-reviewed literature, several papers examined the role of policy in reducing alcohol-related liver disease morbidity and mortality.[66-70] Other alcoholic liver disease interventions include approaches in the clinical field (transplantation, pharmacological treatment[71], long-term management of alcoholic liver disease[72]). However, the focus of the review is on public health and population interventions which are upstream of such patient-focussed options.

Fiscal policies

Taxation

Alcohol price increase has been established as a way of impacting consumption[73], mortality[74] and also healthcare costs.[75 76]

Three dominant tax structures are used internationally, either singly or in combination: (1) ad valorem tax (proportionate to product value); (2) volumetric tax (based on product strength/ethanol content) and (3) unitary tax (based on product volumes).[77]

Sheron *et al.* (2011) highlighted the 'four Ps' as crucial policy areas: pricing, place of sale (availability), promotions, and products.[66] Price-related policies received the most attention in the literature we obtained. Target outcomes for alcohol policies included mortality from liver disease, which provides a good indication of policy success, but also hospital admissions; alcohol-related crime (e.g. assaults, drink-driving arrests); alcohol-related accidents and fatalities and alcohol-consumption itself.

Nelson and McNall (2016) reviewed findings from natural experiments in nine countries to explore the effect of a range of (mostly price-related) policies on alcohol-related harm including: excise duty; quotas for tax-free imports; minimum age limit changes for buying alcohol; taxes; retail limits; advertising bans; drink driving campaigns; legalisation of previously banned types of alcohol.[67] Their findings were mixed; effects varied across countries and sub-groups. The authors concluded that price-related policies may only be successful if the intended population targets are responsive to price changes. They argue for targeted rather than blanket policies, although it should be stated that their research is industry sponsored.

The OECD report on Tackling Harmful Alcohol Use highlights excise duties and value added taxes as the most common combined approach. They mention the limitation of such policies, including potential substitution effects (a minority of consumers are likely to substitute or

complement consumption with a range of intoxicants[78]) triggered by price changes; and the potential reduction in the relative weight of alcohol taxes as a proportion of beverage prices, if they are not indexed for inflation, which may diminish their effects on consumption.[32] Northern European countries, including Finland, Sweden, Norway and Iceland, as well as the United Kingdom and Australia, consistently rank in the upper tertile of taxation for all alcoholic beverages.

On the other hand, the mildest alcohol taxation regimes are found in Southern European countries, including Italy, France, Spain and Portugal; in central European countries such as Austria, Switzerland and Germany; and in the United States.[32] The effect of increased alcohol taxation on consumption depends on the degree to which the tax is passed on to consumers and the OECD report also presents studies showing how different population subgroups respond differently to price changes: moderate drinkers compared to heavy drinkers, women compared to men and adults compared to younger people are more responsive to a price change in terms of modifying their consumption of alcohol.

In addition, different types of alcohol vary in how well consumers respond to price changes (a lower elasticity for beer than wine and spirits) was found in Wagenaar ***et al.'s*** (2009) meta-analysis of alcohol prices.[73]

Price regulation

Minimum unit pricing (MUP), which aims to reduce the availability of very cheap alcohol by increasing its price is another price-related policy discussed in several studies and reports.[32] [66] [70] A similar model (minimum pricing per litre of alcohol, regardless of ethanol concentration) was implemented in the Canadian province of British Columbia in 2002. Since the policy was enacted there have been dramatic reductions in liver disease mortality, despite increasing densities of private liquor stores during the same period.[79] The results of modelling studies have also been supportive of minimum unit pricing as an effective method for reducing alcohol related deaths and hospital admissions. The estimated policy effect on hospital admissions and mortality is 45 times greater than the United Kingdom's existing ban on 'below cost selling'.[80] Furthermore, reduced consumption and spending on alcohol, as well as health and quality of life gains are estimated to disproportionately benefit those on the lowest incomes.[81]

The OECD's report on Reducing Harmful Alcohol use dedicates a chapter to the questions of how minimum unit pricing for alcohol affects different types of drinkers. It confirms that potential detrimental impact of MUP on moderate drinkers of low income is not proven, as their levels of purchasing result in relatively small effects in response to this policy. Low-income heavy drinkers appear to be the group that may be most affected in terms of changing consumption, whereas high income heavy drinkers may be able to afford to maintain harmful drinking patterns.[32] For this reason, MUP is considered to be the fiscal policy which is most likely to reduce alcohol-related health inequalities, and this policy has recently (November 2017) been enacted by the government of Scotland, after a long and highly publicised battle after a legal challenge led by the Scotch Whisky Association.[82]

See Table 5 and Table 6 for an in-depth summary of studies estimating the effect of alcohol policy scenarios, modelling studies, natural experiments and case-studies, respectively on alcohol consumption, hospital admissions and liver disease mortality.

We identified three studies that modelled the effects of different alcohol policy scenarios on liver disease outcomes; all were from the United Kingdom (see Table 5).

- We restricted reporting of outcomes to alcohol consumption, hospital admissions and liver disease mortality.
- Results were strongly supportive of minimum unit pricing as a strategy to drive down alcohol consumption, hospital admissions, and liver disease deaths in the United Kingdom, with the added advantage that the poorest and most vulnerable sections of society were likely to benefit the most.
- If the United Kingdom were able to emulate trends in liver disease deaths seen in France, or Italy, mortality would drop substantially over 10 years.

One study modelled the effects of different alcohol policy scenarios on health inequalities, using total mortality rates. Strength-based taxation and minimum unit pricing were expected to have greater effects on mortality among drinkers in routine/manual occupations and for heavy drinkers in this group in particular.

We identified six studies that used natural experiments or country case studies to demonstrate possible policy impacts on liver disease (see Table 6).

- Again we restricted reporting of outcomes to alcohol consumption, hospital admissions and liver disease mortality.
- Countries included were: Denmark, Sweden, Finland, Iceland, Russia, Hong Kong, USA (Alaska), Canada (British Columbia).
- Altering alcohol taxes were inconsistently associated with mortality, although in the majority of cases the higher the tax the lower the mortality. There was variation by country, by cause of liver death (chronic or acute), by sex, and by length of time since policy implementation. There were also age and birth cohort effects.

It should be noted that many studies rely upon natural experiments to evaluate policies which can provide useful insight into effectiveness. Potential limitations of these study designs are biased findings (e.g. due to lack of control over confounding factors such as other policies working against alcohol policies, non-randomisation if the design includes a control group, lack of assessment of the quality of policy implementation, and because the heaviest drinkers tend not to be captured in survey data).[67 83] Modelling the effects of alcohol related policies is another useful evaluation approach, however the quality of the evidence will depend on the integrity of the underpinning data (e.g. self-reported drinking may be more prone to bias, and it is not always possible to predict the influence of other policies operating simultaneously, or changes in societal practices).[80]

One prominent study included here is industry sponsored,[67] and provides potentially biased inclusion/exclusion criteria and returned articles (e.g. one of the two databases they searched is a resource developed by the International Alliance for Responsible Drinking/International Agency for Research on Cancer [84]) as well as potentially biased interpretation of results.

Table 5. Alcohol policy scenarios and modelling studies: effect estimates for alcohol consumption, alcohol-related hospital admissions and liver disease mortality*

Author & date	Country	Policy description or scenario	Years	Method	Relevant Outcome(s)	Key findings	Notes
Sheron et al (2011)[66]	England and Wales	Black scenario: liver disease deaths continue at same rate as for the last 10 years (increasing)	2008-2019	2008 Office for National Statistics data were used as baseline and projected to 2019 according to each scenario.	– Deaths from liver disease	N=8900 additional deaths	The authors also estimate that there would be 77,000 extra liver deaths in the black scenario compared to the green over 20 years in England and Wales; 80% would occur in people <65 years. Allowing for broader alcohol harms (not just deaths from liver disease) this number increases to between 160,000 and 250,000 deaths.
		Green scenario: liver disease deaths modelled on France's rate of change (decreasing)				N=22,000 fewer deaths	
		Amber scenario: liver disease deaths modelled on Italy's rate of change (decreasing)				N=13,000 fewer deaths	
		Red scenario: liver disease deaths modelled on EU's overall rate of change (decreasing)				N=8900 fewer deaths	
Brennan et al 2014[80], in Rowe 2017[70]	United Kingdom	Scenario 1: Ban on below cost selling.	2014-2015 to 2024-2025	Sheffield Alcohol Policy Model (version 2.5): models 'a linked series of policy outcomes for 96 population subgroups defined by sex, age, annual income, and consumption level'.	– Alcohol consumption – Alcohol related hospital admissions – Alcohol-related deaths	– 0.08% reduction in mean annual consumption amongst harmful drinkers or 3 units per person/year – 500 hospital admissions averted/year – 14 deaths averted/year	In relation to the minimum unit pricing policy: '89% of estimated deaths saved per annum are estimated to occur in the 5.3% of people who are harmful drinkers'
		Scenario 2: £0.45 Minimum Unit Pricing.				– 3.7% reduction in consumption or 137 units per person/year – 23,700 hospital admissions averted/year – 624 deaths averted/year	
Holmes et al 2014,[81] in Rowe 2017[70]	England	Scenario: £0.45 Minimum Unit Pricing.	2014-2015 to 2024-2025	Sheffield Alcohol Policy Model version 2.6. As version 2.5 above, but incorporates price elasticity data from longitudinal studies rather than cross-sectional.	– Alcohol consumption – Alcohol related hospital admissions – Alcohol-related deaths Reported overall, and disaggregated by occupation, income, and type of drinker.	– Overall 1.6% reduction/year or 11·7 units less per drinker/year. – Harmful drinkers: 3.7% reduction/year or 138·2 units less per drinker/year – Overall 29,900 hospital admissions averted/year; amongst routine or manual workers averted admissions =25,700 – Deaths averted = 860; deaths averted amongst routine or manual workers= 710.	'Harmful drinkers on low incomes purchase more alcohol at less than the minimum unit price threshold compared with other groups, they would be affected most by this policy. Large reductions in consumption in this group would however coincide with substantial health gains in terms of morbidity and mortality related to reduced alcohol consumption'
Meier et al 2016[76]	England	Four scenarios equalised to achieve 4.3% population–wide reduction in total alcohol-related mortality Scenario 1: Current tax increase: of 13.4% for all beverage categories Scenario 2 : Ad valorem tax: additional 4.0% alcohol-specific sales tax on product value after duty at the time of purchase (standard 20% VAT is also charged on	2014/2015	Sheffield Alcohol Policy Model version 3.	– Consumer spending – Alcohol related deaths	Large differences in heavy drinkers for how mortality gains are distributed across socioeconomic groups with different policies. – Volumetric tax and MUP give largest consumption reduction among heavy drinkers and have steepest income gradients for consumption effects	United Kingdom unit = 8 g ethanol Authors note that the differential impacts of the modelled policies are partly explained by substantial subgroup variation in baseline alcohol consumption, baselined spending and beverage category preference.

		product) Scenario 3 :Volumetric tax: Replace current excise duty with a £0.22 per unit duty for all beverage types Scenario 4 : £0.50 Minimum unit pricing:				– Volumetric tax and MUP in routine/manual occupation perform better than other policies (6.1% and 7.5% mortality rate reduction respectively) – All policies narrow health inequalities but to varying degrees. – MUP narrows the gap between socio economic groups the most	
**We restricted to these policy outcomes as they were the most closely matched to the remit of the EASL project.*							

Table 6. Natural experiments and country case studies examining the effect of alcohol policies on alcohol consumption, alcohol-related hospital admissions, and liver disease mortality*'**

Author & date	Country	Policy context & description	Years	Evaluation design	Methods	Outcome(s)	Key findings	Notes
Room et al (2013)[85] Cited by Nelson & McNall (2016)[67]	Denmark, Finland, Sweden. Northern & Southern Sweden treated separately.	Lowered tax on alcohol and abolished personal quota on alcohol imports (Denmark and Finland). Policies were implemented over 7 months starting late in 2003.	2003 (baseline); 2007 (final follow up)	Natural experiment: Denmark and Finland were intervention areas, Southern Sweden was proximate to intervention areas and other low tax areas, and Northern Sweden was treated as the control area.	Population survey data and registry data were assessed in intervention and control areas at baseline (2003), and for three follow up years (2004-2006). Short terms effects in 2003/4 were assessed relative to the general trend using a one-sample t-test. Longer term effects not assessed.	– Alcohol consumption (registry and self-reported) – Hospital admissions – Deaths	**Estimated alcohol consumption, including un-recorded:** – Denmark: declining percentage points in follow up years compared to baseline (-3.9% to -9.4%). Significant short-term decline (p=0.008) – Finland: increasing percentage points in follow up years compared to baseline (9.6% to-12.0%). Significant short-term increase relative to general trend (p<0.001) – Southern Sweden: 3% increase in 2004, followed by decrease in subsequent years (-2.4% to -9.6%). Short-term effects not statistically significant compared to general trend. – Northern Sweden: decrease 1.6-2.6% followed by increase of 3.6-7.8%. Short-term effects not statistically significant compared to general trend. **Alcohol-relevant hospitalisation:** – Denmark: Variable change from -2.3% to +2.1% compared to baseline. Short-term effect not statistically significant compared to general trend. – Finland: 5.3-8.6% increase compared to baseline. Significant short-term increase relative to general trend (p<0.001) – Southern Sweden 0.7-6.1% increase compared to baseline. Short-term effect not statistically significant compared to general trend. – Northern Sweden 4.2-7.4% increase compared to baseline. Short-term effect not statistically significant compared to general trend. **Alcohol-specific mortality:** – Denmark: 0-6.8% increase compared to baseline. Short-term effect not statistically significant compared to general trend. – Finland: 18.0-33.6% increase compared to baseline. Significant short-term increase compared to general trend (p<0.001) – Southern Sweden. Variable pattern: 7.1% decrease to 2.1% increase relative to baseline. Short-term effect not statistically significant compared to general trend. – Northern Sweden: 2.4-7.2% increase compared to baseline. Short-term effect not statistically significant compared to general trend.	– Authors conclude that: 'in high-income countries the increase in alcohol affordability during the last decades has already increased total alcohol consumption to the level where further increases in affordability may no longer substantially increase consumption.' – Additional analysis of Finnish data showed socio-economic status (SES) differences: e.g. greater increase in mortality in women (31%) compared to men (16%), and in the 50-59 age group, and largely affecting lower SES groups, and people living alone. (Herttua et al 2008[86] & 2011[87], cited by Nelson & McNall (2016)[67].
Chung et al (2014)[88] Cited by Nelson & McNall	Hong Kong	Alcohol tax cuts (1984), tax increase (1994), two tax cuts (2007 & 2008)	1981-2010	Country case study: assessing long-term, population trends.	Age-Population-Cohort analyses (APC). Authors used sex-specific Poisson APC models.	Alcohol-related mortality (chronic, acute, all, 100% attributable)	– Age effects: alcohol-related mortality (ARM) tended to increase with age until 70 years for acute, 55 years for chronic, and 60 years for all and 100% attributable ARM, at which point it decreased. – Period effects: Acute ARM increased after 1986-1990, decreased after 1996-2000 (men only); Chronic and all ARM increased after 1986-1990, decreased after 1996-	Data are not fully extractable (graphical form without labels). Increased acute ARM in men in 1986-1990 coincided with 'surge of alcohol imports '. Less apparent increase for chronic ARM as it takes longer to develop.

(2016)[67]							2000, then increased after 2001-2005 – Cohort effects: Acute and all ARM increased for both sexes in people born late 50s-early 60s; decreased amongst those born in mid-70s; chronic increased in those born mid-60s, decreased if born mid-70s.	1994 tax increase and decreased imports coincided with declining ARM in both sexes Tax cuts of 2007-8 coincided with increase in acute, chronic and all ARM. Chronic effects may be related to 1984 policy. People born in 1950s and 60s most at risk.
Wagenaar et al, 2009[73], Cited by Nelson & McNall (2016)[67]	Alaska, USA	Two increases in tax 20 years apart (1983 and 2002)	1976-2004	Quasi-experimental design (other states as controls)	ARIMA modelling	Alcohol caused and alcohol related mortality	**Alcohol-caused mortality:** – 1983 tax increase → a 29% reduction in deaths, equal to 23 deaths averted/year – 2002 tax increase → an 11% reduction in deaths, equal to 21 deaths avoided /year **Alcohol-related mortality:** – 1983 tax increase → a 23% reduction in deaths – 2002 tax increase → a 13% reduction in deaths	
Tyrfingsson et al, 2014[89], cited by Nelson & McNall (2016)[67]	Iceland	Life of beer ban in 1989	1982-2009	Country case study using historical death data from Iceland grouped as follows: 1982-88, 1989-95, 1996-02, 2003-09	Spearman's Rank Correlation Coefficient. Rate ratios also reported.	– Liver cirrhosis mortality by cause: – Chronic liver disease – Alcoholic liver disease – Mental & behavioural disorders due to alcohol	– Chronic liver disease deaths (reference=1982-1988): no significant change for females. Significant increase amongst males (RR =2.16, 95%CI=1.07–4.35) for the period 2003-2009 only. – Alcoholic liver disease deaths (reference 1996-2002): no significant change for females. Significant increase amongst males for the period 2003-2009 (RR=2.34, 95%CI=1.09–5.02). – Mental and behavioural disorders due to use of alcohol: • Women (reference 1989-1995): Significant increase for the period 1996-2002 only (RR= 7.73, 95%CI=1.07–339). • Men (reference=1982-1988): Significant increase for the period 2003-2009 only (RR= 3.08, 95%CI=1.05–9.01).	
Khaltourina et al, 2015[90], cited by Nelson & McNall (2016)[67]	Russia	1998-1999: 47% real-term decrease in vodka excise and taxes 2004: 6% increase above inflation in excise tax on spirits 2006: Amendments and regulations governing alcohol sales, production and transportation.	1998-2013	Country case study using historical mortality data	Descriptive and correlational analysis	No of deaths from alcohol poisoning Working age male mortality	– Trend in alcohol poisoning deaths: Sharp increase after 1999, further increases to 2002. Starts to decline from 2003. Sharp declines 2005-2007, continues to decline to 2010. – Correlations – alcohol poisoning deaths with: • Production of ethyl alcohol from crops (millions of decalitres) r=0.89, p<0.001. • Production of vodka and liquor (millions of decalitres) r=0.52, p=0.05 • Sale of vodka and liquor (millions of decalitres) r=0.77, p=0.001. • Per capita GDP: r=-0.58, p=0.03 – Trends in working age male mortality: Substantial increase in 1999 continues to increase up to 2003. Slow decline 2004-2005, sharp decline 2006-2007; decline continues to 2010. – Correlations – working age male mortality with: • Production of ethyl alcohol from crops (millions of decalitres) r=0.94, p<0.001. • Production of vodka and liquor (millions of decalitres) r=0.70, p=0.006	'Ethyl alcohol production was the strongest correlate of alcohol-related mortality, which is probably due to the fact that ethyl alcohol is used for both recorded and unrecorded alcohol production.'

							• Sale of vodka and liquor (millions of decalitres) r=0.60, p=0.025. • Per capita GDP: r=-0.27, p=0.35	
Zhao et al, 2013[79], cited by Rowe (2017)[70]	British Columbia, Canada	Two potentially conflicting policies: Increases in minimum alcohol prices 2002-2009 & Increases in densities of liquor stores due to part privatisation of alcohol retail sales	2002-2009	Natural experiment	Time series analysis of cross-sectional data from 16 health service delivery areas in British Columbia. Authors used mixed models in their analysis.	– Alcohol Attributable (AA) deaths: – Acute deaths – Chronic deaths – Wholly attributable deaths	**Minimum price of alcohol:** – 10% increase in mean minimum price of alcohol was linked to a 31.7% (95% CI: ±25.73%) reduction in wholly attributable deaths from alcohol (per 100,000 people). – 12 months after policy implementation there was a significant reduction in wholly AA deaths, but not acute or chronic. – 2-3 years after policy implementation deaths from chronic and total AA deaths significantly decreased. 'Inconsistent lagged associations' observed for acute AA mortality. – 18-27 months after policy implementation, acute deaths showed unstable results with a mixture of increase and decreases in deaths. **Density of liquor stores:** – 10% increase in private liquor stores was linked to a 2.5% increase in acute AA (95% CI: ±2.39%), a 2.4% increase in chronic AA (95% CI: ±1.57%) and a 2.0% increase in total AA mortality rates.	
*We restricted to these policy outcomes as they were the most closely matched to the remit of the project **In the case of duplicates (different studies but reporting on the same policy, outcomes and data sources) only one was included.								

Marketing restriction

After tobacco, the marketing of which has been regulated, alcohol is the most dangerous and unhealthy commodity currently marketed in Europe.[91] The landscape for alcohol marketing is changing and uses multiple avenues (radio, television sports events, celebrity endorsements, websites, product placement, social media, and others).[91] 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[92], with elements consisting of:

- Regulation, preferably with a legislative basis for alcohol marketing by:
  - regulating the content and the volume of marketing
  - regulating direct or indirect marketing in certain or all media
  - regulating sponsorship activities that promote alcoholic beverages;
  - restricting or banning promotions in connection with activities targeting young people
  - regulating new forms of alcohol marketing techniques, for instance social media
- Development by public agencies or independent bodies of effective systems of surveillance of marketing of alcohol products.
- Setting up effective administrative and deterrence systems for infringements on marketing restrictions.

A set of reviews on the topic were identified, emerging from a Pan American Health Organization-organised regional network of focal points responsible for alcohol issues in Ministries of Health[91]. See Table 7 for a summary of the publications identified as most relevant for this review. These covered:

Alcohol marketing and youth alcohol consumption[93]: all publications identified found positive associations between exposure to marketing and some measure of subsequent drinking behaviour and/or negative consequences of drinking.

Use of digital media in alcohol marketing[94]: conclusions from the majority of reviewed publications were that there was a need 'for policies to control and restrict alcohol promotion, and especially to protect underage youth from commercial incentives to engage in drinking behaviour'. Proposals included regulatory restrictions on access to websites, website content and requirements to report website usage, supplemented with stronger industry codes and tougher sanctions

Industry self regulation[95 96]: the evidence reviewed indicates that the complaint process for breach of the marketing regulatory code lacks standardization across countries, that industry adjudicators may be inadequately trained and that few complaints are upheld against adverts pre-determined to violate a self-regulatory code. The authors concluded that the current system of self-regulation needs major modifications if it is to serve public health objectives, and more systematic evaluations of the complaint process are needed.

Legislation on alcohol advertising[97]: using the example that the 2015 version of the French Évin law does not appear to protect young people effectively from exposure to alcohol advertising in France.

In addition, the series of papers included specific case-studies on alcohol marketing during sports events, corporate social responsibility and legislation in Caribbean and Latin American countries.

The collaborators on the set of 14 papers concluded that the most effective response to alcohol marketing would likely be a comprehensive ban on alcohol advertising, promotion and sponsorship, in accordance with country constitutional principles. Regulations should be statutory, and enforced not by the alcohol industry, but by a public health agency. A global agreement on the marketing of alcoholic beverages would support country efforts to move towards a comprehensive ban on alcohol advertising, promotion and sponsorship. One such effort can be highlighted as the European Centre for Monitoring Alcohol Marketing, which among other work, collects a database of statutory and non-statutory regulation on alcohol marketing in Europe.[98] Finally, authors concluded that collaboration with other efforts to restrict marketing of potentially harmful products (ultra-processed food, sugary beverages, tobacco for instance) should be encouraged.

Table 7. Reviews and studies on the effects of alcohol marketing and digital marketing on alcohol consumption as well as on regulation of and legislation on alcohol marketing

Author & date	Country	Policy context & description	Years	Evaluation design	Methods	Outcome(s)	Key findings	Notes
Jernigan et al (2017)[93]	Europe, Asia and North America	Alcohol marketing's effects on youth drinking	Publications since 2008	Systematic review	Evaluation of studies including baseline measures of youth exposure to alcohol marketing, updating previous reviews	Validated measures of self-reported drinking behaviour.	– Twelve studies included 35,219 unique participants – Significant associations between exposure to, awareness of, engagement with and/or receptivity to alcohol marketing at baseline and initiation of alcohol use, initiation of binge drinking, drinking in the previous 30 days and/or alcohol problems at follow-up were found in all studies	
Lobstein et al (2017)[94]	Several	Commercial use of digital media for alcohol marketing	Publications January 2000 to December 2015	Narrative review	Evaluation of studies and grey literature on evidence on digital media alcohol marketing effects	Drinking behaviour or alcohol consumption increase	– Forty-seven studies included for review – Five documents supported the hypothesis that exposure to alcohol marketing in digital media is associated with alcohol purchase intentions, drinking patterns or higher levels of alcohol consumption – Marketers state that they target adults, but their material is attractive to younger age groups, and by design or by neglect they allow younger age groups to gain access to their marketing	Publication includes in-depth description also of promotional marketing methods
Noel et al (2017)[95]	Several	Industry self-regulation of alcohol marketing	Not reported	Narrative review	Evaluation of process of reviewing the compliance of industry organisations to the alcohol code.	Information on complaints process in self-regulatory marketing systems and its effectiveness	– Thirty one reports and publications provided information on the alcohol code compliance review process – Current complaint submission systems use non-standardized processes – Few complaints, if any, are upheld by industry review boards even for advertisements pre-determined to contain code violations – No instances of actual penalties being imposed for admitted code violations, other than the removal of an advertisement from further broadcasting	Follows another review on the content of, and exposure to, alcohol marketing in relation to self-regulated guideline, also by Noel et al. (2016)[96]
Gallopel-Morvan et al (2017)[97]	France	Assessment of the French Evin law implemented in 1991 which restricts alcohol advertising	2015	Survey of 6642 school children (mean age17.3 years) using self-administered questionnaire (ESPAD)	Descriptive statistics	Exposure to alcohol advertisements in various locations	– 30% exposure to alcohol marketing almost every day, 38% at least once a week, during the last 12 months – 73% exposed at least once a month in supermarkets in movies (66%), magazines and newspapers (59%), on billboards in streets (55%), and on the internet (54%) – 13% felt like having a drink after having seen the last recalled advertisement and 20% found the advertisement attractive	The law applies to drinks > 1.2% alcohol by volume and containing three core measures; prohibits alcohol advertising through media targeted at young people, but allows other less intrusive media. Product information must only contain factual/informative data and objective qualities. A health warning 'Alcohol abuse is dangerous for health' must appear on all alcohol advertisements.

Managing the alcohol environment:

Longer trading hours are associated with higher rates of alcohol-related harm. Lessons can be learnt from Australia where the introduction of policies to restrict trading hours have resulted in 45.1% and 20.3% reductions in non-domestic assault in the urban areas of Sydney respectively.[99]

To reverse the damaging trends in the United Kingdom for example, it has been suggested by the Foundation for Liver Research and Lancet Commission on Liver Disease that off-licence opening hours should be restricted to between 10am and 10pm. In addition, on-licence trading should be restricted to limit the availability of alcohol after midnight.

The OECD's report discusses how most countries set a minimum legal age for the purchase of alcoholic beverages for both on-trade (e.g. bars, restaurants) and off-trade (e.g. retail) sales.[32]

The implementation of laws setting a minimum age for the purchase of alcohol shows clear reductions in drink-driving casualties and other alcohol-related harms.

A further approach involves restrictions on licensing and outlet opening hours. Regulation of alcohol availability has the potential to produce significant effects on alcohol consumption and health outcomes.[100] [101] While extending times of sale can redistribute the times when many alcohol-related incidents occur, such extensions generally do not reduce the rates of violent incidents and often lead to an overall increase in consumption and problems. Reducing the hours or days of sale of alcoholic beverages leads to fewer alcohol-related problems, including homicides and assaults.

However, a stringent policy on alcohol availability should be always coupled with effective enforcement, as informal market activities are likely to develop as a side effect.

Screening and behavioural interventions

Trials have been conducted to evaluate the impact of screening and brief interventions for reducing harmful drinking in European settings.[102] Screening for alcohol misuse can take place in various settings, including primary care and emergency departments. There appear to be limitations to screening for alcohol misuse in emergency departments.[103] In a recent study of a universal testing policy to screen unselected acute medical admissions for alcohol misuse, nurses recorded alcohol consumption in all acute admissions to a large hospital by asking patients about the type of alcohol consumed, frequency and maximum daily amount; and they recorded whether the admission was alcohol related. Scoring allowed identification of individuals at higher risk of alcohol abuse, which led to automatic referral to either a brief intervention or an alcohol specialist nursing service. Researchers found that they managed to identify individuals at high risk of alcohol dependency – providing an opportunity to intervene earlier. Limitations include resources, and that such a setup requires systems to forward patients on to services: Alcohol Specialist Nursing Service; or Alcohol Intervention Team.[104]

The primary goal of behavioural interventions for alcohol misuse is to eliminate risky drinking practices (for example, by encouraging fewer drinks per occasion or not drinking before driving) rather than to achieve abstinence.

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.[102]

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 12month follow-up in primary health care and emergency department trials.[105] In primary health care, brief interventions resulted in 31g/week reduction in alcohol intake after 12 months, and 18g/week for interventions in emergency departments.

The method of delivery of the brief intervention can vary. In one pragmatic cluster randomised controlled trial, all patients received feedback on their hazardous or harmful drinking status immediately after the screening process. However, neither brief advice nor brief lifestyle counselling resulted in a significant reduction of harmful drinking compared with providing patients with an information leaflet.[106]

One abstinence study from Spain[107] conducted a cohort study of patients who were candidates for liver transplant, on the condition that they abstained for six months prior. Factors that were associated with stopping alcohol immediately upon diagnosis of alcohol related liver disease were: family recognition of the problem (odds ratio 3.81, 95%CI=1.27; 11.41) and awareness of alcohol toxicity (odds ratio 5.84, 95%CI=1.31; 26.11). Factors associated with abstaining for 6 months prior to liver transplant were: stopping alcohol at diagnosis of alcohol related liver disease; awareness of alcohol toxicity, and family recognition of problem.[102] A sub-group analysis of patients drinking alcohol-free beer found weak evidence that a greater proportion were able to abstain for six months compared to those not drinking alcohol-free beer (34% vs 20%).

A recent Cochrane review found that personalised digital interventions may be effective for reducing hazardous and harmful alcohol consumption in community-dwelling populations.[108]

There remain unanswered questions around the effectiveness of brief alcohol intervention across different settings, different population groups, about the optimum intervention content, and the longevity of intervention effects. However, available evidence suggests that time-pressed clinicians looking for maximum impact with minimal input should direct their efforts to the delivery of short, simple interventions which focus on prompting individuals to record their alcohol intake, and that these are likely to be most effective in middle-aged, male drinkers.

Interventions to reduce obesity

Background

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-sectoral action,[109] as demonstrated by the following obesity systems map produced as part of the Foresight: Tackling Obesities project in the United Kingdom:[110]

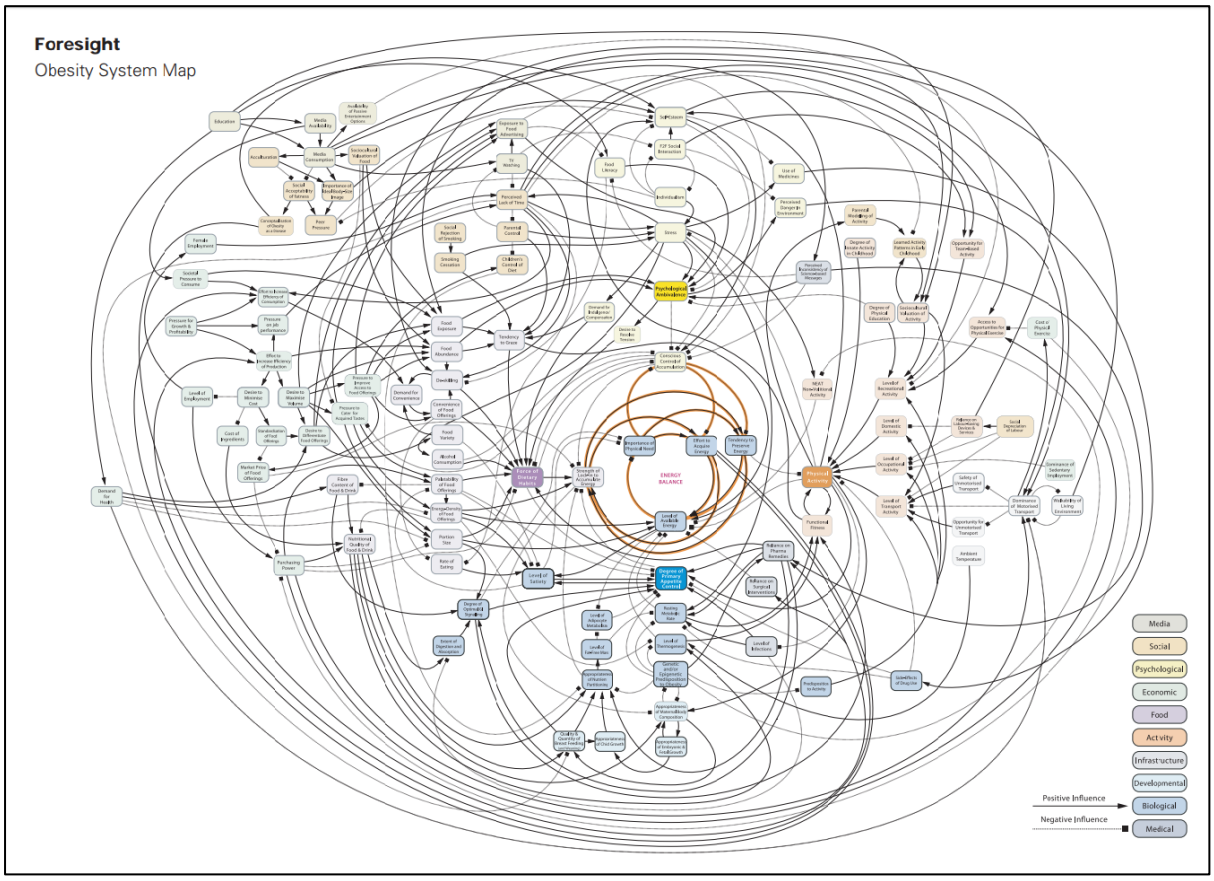


Figure 76: Obesity System Map, United Kingdom Foresight project

We again reviewed a series of reviews and relevant specific obesity focused studies. Specifically, we summarise work by the World Health Organization[111], Harvard university[112], the Heart Foundation Australia[113] and the United Kingdom National Institute for Health and Care Excellence (NICE).[114] 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. This section is divided by level of intervention: policy/population level, community-based, individual level behavioural interventions. We acknowledge that policies including breastfeeding are important for wider non-communicable disease (NCD) prevention[115] but are not covered here.

Policy/population level approaches

Adjusting the food environment

1. Marketing of unhealthy foods and non-alcoholic beverages to children

Marketing of food predominantly promotes the purchase of high fat, salt, and sugary foods.[116] Their long shelf life and cheap production cost are incentives for the food industry to increase the sale of these foods.[117] In their review of the evidence, 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 reducing the prevalence of childhood obesity[118 119] and related NCDs.[120] 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.[121]

2. Nutrition labelling - provision of nutrition information, in a standardised format, on foods sold

Evidence suggests that nutrition labelling enables consumers to make healthier food choices.[122] Nutritional labelling that guides a consumer's understanding, in particular 'traffic light labelling' was cited by 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.[123]

3. 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.[124 125] 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.[126] 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 (Table 8 below) and disease outcomes.

Table 8. Summary of main findings of meta-review of systematic reviews on fiscal policies on diet

	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 nutritients; 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 sugar-sweetened beverages. Limited evidence for disease outcomes.	Disease outcome affected by substitution – nutrient profile taxes less likely to have unintented 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 wealthy. Targeted low-income subsidies effective.

Source: Fiscal policy options with potential for improving diets for the prevention of noncommunicable diseases (NCDs) (draft). Geneva: World Health Organization; 2015.

A longitudinal study from China found that increases in the prices of unhealthy foods were associated with decreased consumption of those foods[127], while in the US programmes to reduce the price of healthy foods resulted in a 78% increase in their consumption.[128]

Modelling studies suggest that a combination of both is optimal (i.e. increasing the cost of unhealthy foods, while also decreasing the cost of healthy foods) particularly in lower income groups where obesity is often higher and the need for intervention greater.[129 130] The United Kingdom Health Forum, in collaboration with Cancer Research United Kingdom, used a simulation model to quantify the impact of a 20% SSB tax on BMI, NCDs and related health costs in the United Kingdom. They found that a 20% tax could prevent 3.7 million cases of obesity and 25,498 cases of BMI-related disease over the next 10 years (2015-2025), and avoid £10million in National Health Service costs in 2025 alone.[131]

While the majority of evidence for effectiveness comes from natural experiments, controlled trials, and modelling studies, as opposed to impacts following implementation, one recent systematic review explored consumption and health outcomes of fiscal measures that have actually been implemented.[132] They found 18 studies, 13 of which were from high income countries, four from upper middle-income, and one from a lower middle income country. They reported significant impacts of subsidies on fruit and vegetable intake and health but not on BMI; significant impacts of sugar-sweetened beverage (SSB) tax on consumption in children, though mixed results for BMI. However, it is possible that the implementation of an SSB has not yet had long enough to have its full impact on BMI and related NCDs. Hall and colleagues[133] report that approximately every change of 100kJ per day will lead to an eventual weight loss of 1kg, with 95% of the weight loss achieved in approximately 3 years, - 50% and 45% achieved in the first and second years respectively, and the final 5% being achieved between the third and tenth years. Therefore, response to a change in energy intake is slow, and the impacts of an SSB tax have yet to be fully played out in observed data.

4. Food reformulation

Food reformulation is the reduction of salt and calories from sugar and saturated fat in processed foods or the increase of beneficial nutrients such as fibre, fruit, vegetables, and wholegrains. There is a lot of variation in the levels of salt, calories, fat, and sugar within many of the regular foods that we eat each day e.g. bread, cheese, sausages, drinks, and cereals. Therefore, adjusting the levels of sugar or saturated fats in these foods could impact the number of calories consumed across the population and potentially reduce (or halt) rising obesity. However, food reformulation is complex and requires collaboration between governments, industry, research, and public health organisations. In addition, a slow decrease (or increase) in nutrients is required to successfully shift population tastes.[134]

In their rapid evidence review, the Heart Foundation of Australia[113] explored the effectiveness of food reformulation as a strategy to improve population health. The majority of the 123 studies included evaluated the impact of sodium reduction programmes, with fewer studies evaluating the impact of reducing saturated fats[135] and transfats[136]. For example, Finland implemented a programme whereby processed food was reformulated to include less salt. This achieved a 3g salt reduction in average intake between 1979 and 2002, along with reductions in average blood pressure which has been attributed to this dramatic reduction in salt intake via reformulation.[137] In another example, the Mauritius government implemented an intervention to replace palm oil with soybean oil as the most common cooking oil in 1987. Over the 5-year follow-up period a reduction in adult cholesterol concentrations, a 5.5% increase in polyunsaturated fatty acids of total energy intake and a 3.5% reduction in saturated fats of total energy intake was observed in a

sample of 5000 participants.[138] As well as providing health benefits, such reformulation programmes have been shown to be cost-effective.[139-141]

The Heart Foundation of Australia found little or no information on the reformulation of fibre, wholegrains, fruit, vegetables or calcium. To our knowledge, no systematic review of the impact of sugar reformulation programmes exists, however one is currently in progress.[142]

One modelling study has quantified the impact of gradually reducing sugar in soft drinks (without substitution) on the prevalence of overweight, obesity, and type 2 diabetes.[143] Using the National Diet and Nutrition Survey in the United Kingdom, the authors estimated baseline average consumption of SSBs and their contribution to total energy intake. For the scenario, they estimated the reduction in this baseline energy intake resulting from a proposed 40% reduction in free sugars added to SSBs over 5 years. Results predicted that this would lead to an average reduction in energy intake of 38.4kcal per day by the end of the fifth year and a 1.20kg reduction in adult bodyweight. This results in a reduction in the prevalence of adult overweight by 1% and obesity by 2.1% which is equivalent to around 0.5 million overweight and 1 million obese adults. Such changes will also result in a subsequent reduction of 274,000-309,000 new cases of type 2 diabetes over the following 20 years.

Social marketing

WHO found limited data for the effectiveness of social marketing campaigns, especially around promotion of healthy diets.[144] However, intensive use of mass media to advocate for a specific aspect of the diet e.g. increasing fruit and vegetables has been shown to be most effective. Further, social marketing in combination with 'upstream' policies e.g. taxes, or 'midstream' community based interventions are more likely to be most successful.[145]

Community based interventions

WHO propose that weight management interventions are effective if they are adapted to a local context.[144] Interventions embedded within local culture, involving key stakeholders (e.g. community leaders), and using existing social structures such as community, schools systems, and weekly meetings with older adults make implementation easier. The EPODE study[146] and OPIC study[147] are key examples.

School-based interventions

Amini *et al.*(2015)[148] found mixed results in their review of eight reviews of 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 to 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. For example, one review[149] found that 10 out of 12 studies which used at least two of the three most common components (classroom activities, parental involvement, school nutrition policy) were effective in reducing overweight and obesity. However, given that results were inconsistent in their effectiveness across the reviews, the authors did not favour one component over another. Duration was found to be crucial to the

effectiveness of school-based interventions; however few studies assess the length of time required.

Individual and family-based interventions

Individual behavioural interventions

Both WHO and NICE recommend the use of multi-component lifestyle interventions (MCLI) which typically include components such as diet, physical activity, and educational/cognitive.[144] [150] Johns and colleagues (2014) carried out a systematic review and meta-analysis to examine the clinical effectiveness of different types of interventions: diet or exercise alone versus combined behavioural weight management programs (BWMP).[151] Eight studies met the inclusion criteria because they were randomised controlled trials (RCT) of combined BWMPs compared with diet-only or physical activity-only in overweight or obese adults with at least 12 months follow-up. They found no significant difference in weight loss from baseline or at 3 to 6 months between the BWMPs and diet-only arms (-0.62 kg; 95% CI: -1.67; 0.44), but a significantly greater weight-loss in the combined BWMPs (-1.72 kg, 95% CI -2.80; -0.64) at 12 months. For BWMPs compared with physical activity, there was a significantly greater weight loss in the BWMP at 3 to 6 -5.33 kg, 95% CI: -7.61;-3.04) and 12-1 8months (-6.29 kg, 95% CI: -7.33;-5.25).

In their review, Vetter *et al.* (2010) reported that a comprehensive program of lifestyle modification, comprised of diet, physical activity and behaviour therapy, results in an average weight loss of around 7-10% of initial weight in obese individuals, with two trials reviewed observing a substantial decrease in the risk of type 2 diabetes.[152] However, in their review of behavioural weight management programmes delivered in routine practice, Hartmann-Boyce *et al.* (2014)[153] found no evidence of statistically significant difference in weight change between intervention and control groups at 12 months (mean difference-0.45 kg, 95% CI: -1.34; 0.43). Nevertheless, significant weight loss was observed from pooled estimates of commercial weight loss studies compared to controls (mean difference −2.22 kg, 95% CI: −2.89; −1.54 at 12 months). The authors concluded that interventions delivered by experts may achieve much better results than those delivered in routine practice; however it was unclear why this would be the case.

A known issue with individual weight management programmes is that weight is frequently regained once the intervention stops.[154] However, even small losses in weight can have an important impact on population health over the long-term, but weight maintenance programmes (following weight loss) in addition to weight loss programmes themselves are recommended (NICE).[155]

NICE provided a set of best practice principles on the management of obesity in primary care in the United Kingdom[156] that may be applicable in other countries:

The best practice principles identified in NICE guidance on management of obesity are:

Primary care organisations and local authorities should recommend to patients, or consider endorsing, self-help, commercial and community weight management programmes only if they follow best practice [4] by:

- helping people assess their weight and decide on a realistic healthy target weight (people should usually aim to lose 5–10% of their original weight)
- aiming for a maximum weekly weight loss of 0.5–1 kg
- focusing on long-term lifestyle changes rather than a short-term, quick-fix approach
- being multicomponent, addressing both diet and activity, and offering a variety of approaches
- using a balanced, healthy-eating approach
- recommending regular physical activity (particularly activities that can be part of daily life, such as brisk walking and gardening) and offering practical, safe advice about being more active
- including some behaviour change techniques, such as keeping a diary and advice on how to cope with 'lapses' and 'high-risk' situations
- recommending and/or providing ongoing support.

Figure 77: Best practice principles of obesity management in Primary Care, United Kingdom (NICE)

Family-based behavioural interventions

NICE found strong evidence from eight randomised controlled trials that child/adolescent and parent weight management interventions result in significant decreases in BMI, and are more favourable than child-only programmes. An example of the type of interventions reviewed is DeBar *et al's.* (2012) RCT on a MCLI in primary care for overweight adolescent females in the USA.[157] The females (N=208) were aged 12-17 years old and the intervention included 16 group sessions, in-session yoga, dance video games and play stations to families to improve physical activity, as well as 12 group sessions for parents, health education and psycho-educational materials. In addition, teens received ongoing feedback from their GP. The sample was followed at 6 and 12months post intervention. The decrease in BMI z-score over time was significantly higher for the intervention (-0.15) versus 'usual care control group' (-0.08).

NICE also found strong evidence from 17 studies (United Kingdom, USA, Australia, Italy) that whole family-based interventions for overweight or obese children and adolescents resulted in significant decreases in BMI z-score whether directed at individual families or group based.[150] Fifteen of 17 of these studies assessed the effectiveness of multi-component lifestyle interventions specifically. An example would be the 'Mind, Exercise, Nutrition, Do it' (MEND) intervention.[158] This is a 12-week programme, including 18 two-hour educational and physical activity sessions for parents and children held twice weekly followed by a 12-week free family swimming pass. Follow-up at 6 and 12 months post-intervention found a significant reduction in BMI z-score (-0.24; P<0.0001) and waist circumference (-0.37; P<0.0001) in the intervention group as compared to controls.[158]

Very low energy diets

Very low energy diet (VLED) is defined as a diet of less than 3347 KJ/day (<800 kcal/day).[159] They often consist of synthetic and food-based formulas that provide a rich source of protein supplemented with vitamins and minerals. One systematic review[160] of 32 studies of VLED found 13 studies reporting significant weight change at the end of VLED. Study follow-ups varied from one to five years, and 15 studies reported significant weight changes from baseline at follow-up. Maintenance of weight loss was found to be supported by exercise,

behaviour therapy and longer reintroduction of VLED post-VLED. Thirteen studies reported waist circumference change, and of these seven reported significant reductions in waist circumference at the end of VLED, and nine studies a significant reduction at study end. The reviewers conclude that studies where VLED is coupled with a conventional diet, exercise and/or orlistat results in greater weight maintenance over time. However, the heterogeneity of the studies including other components (e.g. behaviour therapy, exercise programmes, low fat diets, low-carbohydrate diets, medication (orlistat and sibutramine) or corset treatment) makes conclusions about the long-term effectiveness of VLED difficult.

Interventions to reduce NAFLD

Prevention and management interventions

Since obesity is a key risk factor for NAFLD then the interventions outlined above, if successful, might be assumed to have an impact on the subsequent reduction in NAFLD. However, we found few studies that explicitly explored the impact of obesity interventions on the reduction in NAFLD.

One recent systematic review[161] of randomised controlled trials assessing diet, exercise, or combination interventions aimed at reducing steatosis or markers of NAFLD activity was found. Of the 24 articles that met the inclusion criteria; six assessed weight loss using dietary restriction, 10 assessed exercise, and eight were combination interventions. All of the trials showed a significant reduction in steatosis and/or markers of NAFLD activity, though combination interventions (i.e. low calorie diet with 30-60 mins of exercise 3-5 days a week) were found to be the most effective at improving NAFLD. Specifically, weight loss of 5% in NAFLD or 7–10% in NASH is beneficial, and this should be achieved by a combination of moderate dietary restriction and 30–60 min of moderate-intensity exercise on 3–5 days per week.

Treatments

There are no pharmacological interventions to treat NAFLD.[162] However, in their paper, Townsend and Newsome (2017) make a recommendation for a specialised clinic to manage NAFLD which incorporates input from a multidisciplinary team of hepatologist, diabetologist/weight loss physicians, and dieticians.[163]

Interventions to reduce type 2 diabetes and liver cancer

Type 2 diabetes accounts for 90-95% of all diabetes cases,[164] 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.[165]

The diabetes prevention programme (DPP)[166] has been well evaluated and implemented in a number of countries. The initial RCT[167] divided participants into three different groups: Receiving either a lifestyle intervention, receiving Metformin or a placebo group. The behavioural intervention decreased the risk of developing type 2 diabetes by 58% and the metformin treatment by 31% compared to 11% in the placebo group. The intervention consists of:

1. case managers or 'lifestyle coaches' who make frequent contact with participants,
2. a structured 16-session core-curriculum that teaches behavioral self-management strategies for weight loss and physical activity,
3. supervises physical activity sessions,
4. flexible maintenance interventions and motivational campaigns,
5. tailoring of materials and strategies to address ethnic diversity, and
6. an extensive network of training, feedback, and clinical support.

At 10 year follow-up[168] diabetes incidence rates were about the same across each of the groups (5.9, 4.9, 5.6 per 100 person-years in the lifestyle, metformin, placebo group respectively), however, the cumulative incidence of diabetes over the 10 years was lowest for the lifestyle group (34% lower than placebo). Incidence in the metformin group was 18% lower than placebo. The DPP has subsequently been implemented in a number of countries, including the United Kingdom, India, and Finland.

One systematic review of 17 studies of VLED in diabetic patients[169] found an average weight loss of 13.2kg (4.1-24kg) and mean HbA1c reduction of 1.4% demonstrated that VLED in people with T2D was associated with significant weight loss, reduction in blood glucose profile and improvement in cardiovascular risk profile, high tolerability and good safety outcomes. Studies were heterogeneous and longer term outcome data post VLCD are still required.

The role of Metformin has been investigated in relation to its impact on liver cancer mortality in diabetic patients. In their review, Fujita *et al.* (2016)[170] report on three case-control studies[171-173] that suggested metformin reduced the risk of liver cancer in type 2 diabetic patients. A prospective cohort study[174] demonstrated benefits of metformin for liver cancer prevention in diabetics compared with non-diabetic patients. However, Fujita *et al.* (2016) report on two retrospective cohort studies[175 176] and two meta-analyses[177 178] (the latter on randomised controlled trials) that found no significant impact of metformin on the risk of liver cancer.

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

Background

In 2015, the WHO produced the first guidelines for the prevention, care and treatment of persons living with chronic hepatitis B infection.[179] They highlight the WHO recommendations for:

- the prevention of hepatitis B virus transmission, and focus in particular on the prevention of early childhood hepatitis B virus infection through infant and neonatal hepatitis B vaccination[179]
- prevention of mother to child h transmission using anti-viral therapy
- non-invasive screening of liver disease stage at baseline and during follow up
- prioritising treatment with antiviral therapy and conditions for discontinuation

The WHO also provide guidelines on the screening, care and treatment of persons infected with hepatitis C.[180] These recommendations cover:

- screening to identify persons with hepatitis C virus infection
- confirmation of the diagnosis of chronic hepatitis C virus infection
- screening for alcohol use and counselling to reduce moderate and high levels of alcohol intake
- assessing degree of liver fibrosis and cirrhosis
- assessing for hepatitis C virus treatment
- updated recommendations to replace existing regimens with direct acting antiviral agents (DAAs)

A summary of the recent evidence will be structured following these WHO guidelines, and will focus on evidence and current policies for hepatitis B immunisation, as well as information on the development of hepatitis C vaccines. Evidence for the improvement of access to testing and diagnosis of hepatitis and current evidence and recommendations for treatment are also included. In addition to the WHO's guidelines, other organisations, such as the European Centre for Disease Control[181] and the Lancet Standing commission on liver disease[99] have recently highlighted the need for interventions to reduce harm for high risk groups.

Immunisation

Hepatitis B vaccination

Hepatitis B vaccines are available for vaccination of newborns or adult persons at high risk. They can be administered alone or in combination with other vaccines for infant vaccination. A review of 22 studies including 11,090 persons followed up to 20 years after vaccination found no evidence of chronic hepatitis B virus infection, while the cumulative incidence of subclinical hepatitis B virus infection was 0.7% (95% CI: 0.5%; 1.0).[182] A meta-analysis of 29 randomised controlled trials found that infants who receive the first dose at birth are 3.5 times less likely to become infected when born to infected mothers (RR 0.28, 95% CI: 0.20;0.40), compared to infants who received placebo or no intervention.[183] There is no evidence to support the need for a booster dose of hepatitis B vaccine after completion of the primary vaccination series in routine immunization programmes,[184] and these vaccines are considered to have an excellent safety profile.[185]

The rate of development of chronic hepatitis B virus infection is inversely related to the age at acquisition of the infection, occurring in approximately 80%–90% of infants infected perinatally, 30%–50% of children infected before the age of 6 years, and in <5% of infections occurring in otherwise healthy adults.[10] WHO recommends that all infants receive their first

dose of hepatitis B vaccine as soon as possible after birth. The birth dose should then be followed by two or three additional doses with a minimum interval of four weeks.[186] WHO recommends hepatitis B vaccination of persons at high risk of hepatitis B virus infection in older age groups and catch-up vaccination of unvaccinated cohorts if the necessary resources are available.

A systematic review was conducted to assess the evidence on economic evaluation of hepatitis B vaccine in low and middle income countries. Since introduction of the vaccine, 18 of the 19 studies included found hepatitis B vaccination to be cost-effective or cost-saving using GDP per capita thresholds. Five of six studies of birth vaccination also showed it was cost-effective, regardless of endemicity.[187] Another systematic review on the topic identified 22 articles, including nine, five and eight analysing the vaccine's cost-effectiveness, cost-benefit and cost-utility, respectively.[188] While universal vaccination was the subject of most studies in low and middle income countries, in studies on high income countries, the economic evaluations were focused on the implementation of hepatitis B vaccination in specific settings (diabetic, renal and other chronic conditions, and caring centres for patients with sexually transmitted diseases, HIV or hepatitis C, as well as PWID). These studies showed cost-effective results for vaccination in both the infectious and chronic disease fields.[188]

In May 2016, the Global Health Sector Strategy on Viral hepatitis was endorsed by Member States and has set a 2020 target to reduce the new cases of chronic hepatitis B virus infection by 30%, equivalent to a 1% prevalence of hepatitis B surface antigen (HBsAg) among children less than five years of age, and a 2030 target of achieving a 0.1% prevalence of HBsAg mong children five years of age.

Supplementary material for Part 3

Table 18 in the supplementary material summarises the year of first introduction of Hepatitis B vaccination in all 35 countries. As of August 2017 all countries now include hepatitis B vaccination as part of their vaccination schedule. In the United Kingdom, the last country to introduce this for instance, all newborns born on or after 1 August 2017 will be eligible for a hexavalent vaccine, which protects against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and disease caused by Haemophilus influenzae type b.[189]

Hepatitis C vaccination

While new antivirals provide options for improved treatment of hepatitis C virus infections (see below), the majority of infections are asymptomatic, so the majority of infected individuals will not receive treatment and will pose a risk of transmitting the infection to others. An effective hepatitis C vaccine will be important for the successful control of hepatitis C virus infection, would reduce the need for harm reduction services in at-risk populations and could prevent liver cancer and liver failure associated with chronic hepatitis C virus infection. Hepatitis C virus vaccine development efforts are hampered by several immune evasion strategies.[190] Despite this, vaccines are currently being developed, and a few are currently in human studies.[191]

In a modelling study, Stone *et al.* (2016), compared the annual vaccination rates required to reduce chronic prevalence and incidence amongst PWID by 25% to 75% over 20 and 40 years to the annual treatment rates that achieve the same impact in the United Kingdom. They estimated that even low efficacy hepatitis C virus vaccines would have considerable impact on prevalence and incidence among PWID over 40 years, at coverage levels comparable to those for hepatitis B virus vaccination among PWID in the United Kingdom. They found that similar reductions in prevalence or incidence could be achieved with 4-16 or 2-11 times fewer treatments, respectively. The current hepatitis C virus costs, compared to traditional vaccination costs however, would make hepatitis C virus vaccination a much cheaper strategy for reducing hepatitis C virus transmission, compared to treatments.[192]

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

A 2013 systematic review of evidence of the cost-effectiveness of hepatitis B virus and/or hepatitis C virus screening included 29 publications, of which 23 involved Markov modelling, with the remaining presenting costs per case identified or infection prevented.[45] Eligible populations and implementation of screening varied, but the review identified that HBsAg screening of the general population of baby-boomer age and universal antenatal screening and screening of migrants was cost-effective. However, no data on HBsAg screening interventions in PWID, men who have sex with men (MSM), sexual health clinic attendees or prisoners were found.

The review found that fewer studies of hepatitis C virus existed, and that these indicated that screening and treatment of the general population was cost-effective in five out of six studies, as well as screening in the PWID populations. There was limited evidence on the effectiveness of hepatitis C virus antenatal screening, or screening of migrants, prisoners, MSM, or sexual health clinic attendees in United Kingdom (except for patients with >100 lifetime sex partners in the US).

In 2017, the WHO Guidelines on hepatitis B and C testing were published[193] and although aimed at the healthcare planning audience mainly in low and middle income countries, they outline the main recommendations on who to test, how to promote the update of testing and link to further care, for both hepatitis B and C.

Harm reduction

Among PWID, sharing needles/syringes is the main risk factor for hepatitis C virus infection, as well as sharing drug preparation containers, filters, rinse water and back loading (a method of sharing drugs by transferring them from the needle of one syringe into the barrel of another).

Needle syringe programmes (NSP) provide clean syringes and needles as well as condoms to prevent transmission via the blood. These services operate through a range of modalities including via fixed sites, outreach, peer PWID networks, vending machines and pharmacies. Drug treatment for opioid addiction also encompasses these strategies in the form of opioid substitution therapy, as well as psychosocial approaches and residential rehabilitation. Methadone maintenance therapy and buprenorphine maintenance treatment are the most

commonly prescribed opioid substitution therapy (OST). They are consumed orally and so reduce the need for potentially unsafe injections. The impact of these services among PWID on the incidence of hepatitis C virus infection was reviewed[194] in a systematic review of randomised controlled trials, cohort and case-control studies as well as some cross-sectional surveys. They included 28 reports (published and unpublished), which provided information on the impact of OST and/or NSP interventions on hepatitis C virus incidence, but did not identify any RCT.

In 12 studies, OST reduced hepatitis C virus incidence by 49% (95%CI: 37-60%). In the European subgroup of studies, this effect ranged between 32% and 73% reduction. This effect was not affected by differences in study quality, geographical region, or types of study design included (i.e. with or without cross-sectional studies).

There was weaker evidence that a high coverage of NSP reduced the risk of hepatitis C virus incidence (RR 0.79 95%CI: 0.39; 1.61) compared to no or low coverage. However, this protective effect was significant in two European studies. Combination of OST and high coverage of NSP was associated with a 74% reduction in the risk of hepatitis C virus infection (95%CI:11; 93), while there was no evidence of an equivalent protection with OST and low NST coverage in studies in which estimates were provided adjusted for potential confounders.

As no RCTs were identified, the studies were all rated as high risk of bias. The authors also mention that heterogeneity in the effect measures used motivated the conversion of these into relative risks, which could be one source of variation and bias in results. Nevertheless this review confirmed findings from previous reviews that showed consistent and large effects of NSP and OST on injecting risk behaviours associated with blood borne virus transmission.[195]

A similar systematic review of the effectiveness of needle exchange programs for the prevention of hepatitis C virus infection in people who inject drugs however found limited evidence of a protective effect.[196] It should be noted that only six studies were included in the meta-analysis, one of which was excluded from the Platt *et al.*(2017) Cochrane review due to ineligibility (no intervention of interest (NSP shuts down for some of the follow-up) and another which provided incomplete data (did not report 95%confidence intervals around the effect estimate, nor the number of new hepatitis C virus cases in intervention and comparison groups required to estimate it)).

Treatment as prevention

Hepatitis B

Antiviral therapy, with the nucleos(t)ide analogues (NAs such as tenofovir or entecavir is recommended for :all individuals with chronic hepatitis B and clinical evidence of cirrhosis, adults with chronic hepatitis B only, adults over 30 years and with abnormal blood results and adults with evidence of high-hepatitis B virus replication levels. Entecavir is recommended in children aged 2–11 years. NA therapy should be lifelong, and discontinuation should only be considered exceptionally. Monitoring the disease progression and treatment response in chronic hepatitis B infected individuals during and post-treatment is also recommended.[179]

Hepatitis C

As mentioned above, the recent development of new DAAs for treatment of hepatitis C are likely to have an important impact, with preliminary reports suggesting that they provide higher sustained virological response (SVR) rates and lower serious adverse event rates compared to the previous standard care of pef-IFN-α and ribavarin.[180 197] SVR, the lack of detectability of hepatitis C virus in the blood 6 months after completion of antiviral therapy[198], is a proxy outcome for hepatitis C morbidity and mortality, since achieving it seems to be associated with improved clinical outcomes.[199] However, achievement of a short-term proxy blood test result still needs to be validated in terms of long-term clinical outcomes. DAAs consist of four classes of drugs which differ in therapeutic targets, but all target non-structural proteins of the virus, which ultimately affects its ability to replicate and disrupt infection.[200] A recent Cochrane review of 351 references reporting results from 25,232 participants in 138 trials conducted 2004-2016 aimed to assess the benefits and harms of DAAs in people with chronic hepatitis C virus. The authors noted that all studies were at high risk of bias, and more than 40% of these trials assessed DAAs withdrawn from the market or under development. The systematic review and meta-analysis (where sufficient data were available) found no evidence of a difference in the risk of all-cause mortality, no evidence of reduced risk of serious adverse events (except for simeprevir in subgroup analyses by DAA type). However, DAAs were found to decrease the risk of no sustained virological response (relative risk 0.44 (95%CI: 0.37 to 0.52). While the methodology of this review followed stringent Cochrane guidelines and criteria, the findings are limited by the high risk of bias of all studies included, the short-term assessment for most of the outcomes, and the paucity of trials with a sufficient number of participants assessing clinically relevant outcomes that have been conducted.[200]

While conclusions cannot yet be drawn on the clinical benefits of hepatitis C, the positive effect on SVR is likely to contribute to transmission control in a proportion of the infected and treated population. A 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.[201] By developing a disease progression Markov model of hepatitis C virus in the European Union, they forecast hepatitis C virus prevalence and disease burden (i.e. hepatocellular carcinoma, decompensated cirrhosis, and liver-related mortality) over time as a function of the number of diagnosed and treated cases after adjusting for SVR, accounting for influx of migration in recent years. Their model suggests that achieving 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 was estimated to need to be expanded from 88,800 new cases annually in 2015 to 180,000 by 2025. WHO is not making a recommendation regarding this, but guidelines of other organizations (e.g. AASLD and EASL) now recommend that all persons with hepatitis C virus infection should receive treatment.[180]

Data on access to and uptake of DAAs was only available for a selection of European countries.[202] There are 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 estimated prevalent patients. By contrast, the trend in the United Kingdom has been one of slower and lower levels of access. See Figure 84 of the supplementary

material for information on the cumulative percentage of patients treated of the prevalent population between 2012 and 2016.[202]

Screening for liver disease

Late presentation is a feature of a majority of liver disease diagnoses. In light of the fact that therapies are more effective and potentially curative in mild fibrosis and early stage liver cancer, screening for earlier detection of liver diseases, including rare and familial types, is a population-level intervention that may help reduce the burden of liver disease at population level.[203 204] A limited number of reviews on the effect of screening the general population for liver diseases were identified. The options for fibrosis testing include blood tests for indirect markers, ultrasound-based transient elastography and magnetic resonance elastography.[205] Studies have shown that these non-invasive methods are becoming increasingly precise in predicting non-significant and advanced liver fibrosis, but when these values fall, liver biopsy may still be required.

The majority of the literature on liver disease screening focussed on the surveillance for hepatocellular carcinoma in patients with cirrhosis or infection with hepatitis B or C.[206-208] All liver societies endorse the surveillance of cirrhotic patients for liver cancer, and recent models of risk-stratified liver cancer surveillance have been shown to be cost-effective (in Markov models of five year old cirrhotics).[209] Authors of a recent review suggest that emerging technologies (biomarkers and imaging) should be utilised, and tailored screening developed, especially with the development of non-traditional candidates for screening (cured hepatitis C infected, or individuals with NAFLD).[210] A modelling study of assessing the long-term cost-effectiveness of a risk stratification pathway to identify people at risk of developing NAFLD based in a community setting was found to be cost-effective under thresholds for the United Kingdom, where the study took place. Individuals identified from general practice with type 2 diabetes were screened using transient elastography and hepatologists were able to stratify patients at risk of NAFLD.[211]

Metabolic and auto-immune liver disease also offer opportunities for improvement of outcomes and epidemiology through enhanced and earlier diagnosis and screening, but there are limited available markers for some disease (i.e. neonatal Wilson's disease).[212] The development of technology, such as liquid chromatography is hoped to facilitate screening in future years.

One study of generalised population screening in a primary care population (the HEIRS study) concluded that generalised screening for hemochromatosis and iron overloading should not be recommended, and that a role for focussed screening in relevant subgroups may be more appropriate. This serves to highlight that not all liver conditions will be eligible for population-level screening. In one review, aside from the need for a test or examination for the condition, the additional criteria for population-level screening were outlined as: treatment for the condition and facilities for diagnosis and treatment should be available; there should be a latent stage of the disease; the test should be acceptable to the population; there should be an agreed policy on who to treat; the total cost of finding a case should be economically balanced in relation to medical expenditure as a whole and also that case-finding should be a continuous process, not just a 'once and for all' project.[213]

The limited evidence for the effectiveness and cost-effectiveness of screening for liver diseases, both common and those from autoimmune, metabolic or genetic causes, is sparse. One important recommendation is therefore for further work in this area. Some authors suggested that programs to encourage cholesterol testing for the prevention of heart disease, or glycaemia for the diagnosis of diabetes, can provide some guidance for adult screening for liver disease in medical practice.[214]

Summary

The review of reviews on policy for the reduction of alcohol consumption has shown evidence that fiscal policies seem to be the most effective at impacting alcohol consumption, in particular MUP and volumetric taxes. The recent success in passing through legislation on MUP by the government of Scotland will be a concrete example of such policies, and should allow monitoring and evaluation to establish on-going effectiveness. Evidence from the literature is also consistent with the need for a full regulatory approach to alcohol marketing, in particular to children and young adults, with monitoring by public health bodies and consistent enforcement and accountability. Applying these policies will likely have a greater effect if the alcohol environment with regards to spatial and temporal availability is also regulated. Finally, the implementation of evaluated, effective and context-appropriate individual level approaches, of screening and delivery of behavioural interventions may help identify and treat individuals most at risk of harmful alcohol use, thereby having a large impact on reducing alcohol related ill-health, including alcoholic liver disease.

Policy options for the reduction of obesity and type 2 diabetes prevalence also include fiscal policies and these are recommended for reducing all behavioural risk factors for NCDs. There is limited evidence on the long term impact of food taxes, however implementation is relatively recent and modelling studies suggest that a longer follow-up is necessary to observe the full effect. There is good evidence on the effectiveness of combined intervention (low calorie diets plus exercise) in reducing obesity, type 2 diabetes, and potentially risk of NAFLD if delivered in the right setting. However, maintaining this weight loss is difficult, with many individuals regaining weight after the intervention.[154] Family-based multi-component interventions show promise for tackling childhood obesity. The WHO recommends a series of ‘best buys’ for reducing the burden of non-communicable diseases, such are liver disease, via impacting diet and physical activity.[65] These are: reduced salt intake in food, replacement of transfat with polyunsaturated fat, and public awareness through mass media on diet and physical activity.

Hepatitis B and C infection control practices are already in place in a majority of European countries and include hepatitis B vaccination, reducing harmful injecting drug use, as well as screening and treatment for both hepatitis B and C.

Implementation issues, limitations

An important feature in the implementation of public health policies is monitoring and evaluation. Lack of national liver mortality targets are a limitation to the evaluation of policies and intervention. Sheron *et al.*(2011) argue that it is essential for governments to set targets for liver disease mortality to assess policy effectiveness, and to develop new policies. The United Kingdom, for example, does not have a liver mortality target.[66] The quality of policy development and implementation by governments is also susceptible to influence from

powerful alcohol lobby groups. This can result in less effective and poorly implemented policies.[66] An 'alcohol policy scale' similar to the one used by Hadland *et al.* (2015) for the USA could be useful for European countries/regions to monitor policy development and implementation, and policy effectiveness.[69]

Another aspect to implementation is ensuring that any policy implemented is enforced. In a recent study of youth alcohol consumption in Dutch municipalities, integrated interventions with involvement beyond the public health sector, to increase policy enforcement, among other measures, were associated with greater declines in youth alcohol consumption.[215] Similarly, greater reductions in alcohol-related hospital admission rates were observed in areas with more intense alcohol licensing policies (i.e. in local government areas where more intense scrutiny of alcohol licence applications).[216]

An area of improvement in hepatitis control policy includes the development of serological surveys of HBsAg as a proxy for hepatitis B prevalence. These should be representative of the target population, and would serve as the primary tool to measure the impact of vaccination and verify achievement of the hepatitis B control goals. ECDC recommends that reporting and monitoring systems should be strengthened to improve the quality of data on the birth dose of vaccination in order to monitor the coverage and impact of immunisation campaigns.[217]

Multi-level /integrated interventions:

Alcohol consumption and obesity are complex problem requiring a variety of interventions at different levels. The WHO[111] recommends a 'whole systems approach' to act on obesity ensuring that actions are taken in multiple settings and at all levels – government, individual, schools, community, incorporating a variety of approaches and involving a wide range of stakeholders.

In addition, interventions should be sustained at each of these levels, as well as in sectors such as agriculture, food manufacturing, education, transportation, and urban planning. While evidence suggests that each intervention has small effects on its own, WHO argue that together these make up significant parts of a comprehensive obesity strategy.

WHO identify three broad components of population based approaches to obesity prevention:

- Structures in government need to support prevention: such as 'Health in all policies', networking and partnership, monitoring systems for NCDs.
- Population wide policies and initiatives: direct actions such as a childhood obesity prevention strategies which incorporate regulations (taxes and subsidies); and social marketing campaigns.
- Community-based interventions: multi-component interventions and programmes, typically applied across multiple settings, tailored to the local environment and implemented locally.

Similarly, the OECD recommends that combining alcohol policies in a coherent prevention strategy would significantly increase projected impacts.[32]

Research recommendations:

- NICE recommends that studies should use validated methods to estimate body fatness (BMI, waist circumference), dietary intake, and physical activity. This will also apply to

alcohol consumption studies as it will allow for pooling of effects across studies. There is a lack of established benchmarks for a metric of cost per unit change in BMI. NICE also recommends further research into which choice interventions help to reduce increased risk of drinking alcohol (and other unhealthy behaviours).

- There is little evidence on effectiveness and cost-effectiveness of interventions or effectiveness of interventions in non-clinical settings. Programmes and local provision of MCLI should be evaluated and more research is needed on the effect of school-based interventions to control childhood obesity.[148]
- Interventions at a local level i.e. broader community level are not well evaluated, or don't evaluate the impact on health e.g. congestion charge zones making it safer to walk to school. They recommend that all local action consider health in their evaluation.
- Additional research is required on the effectiveness of pharmacological and surgical interventions in people with comorbidities, how interventions vary by age, gender, ethnic, religious and/or social group. (NICE)
- NICE recommends research into accurate and cost-effective non-invasive tests for diagnosis of NAFLD in adults and non-invasive tests for NASH in adults with NAFLD.
- Randomised clinical trials assessing the clinical effects of DAAs are needed. Such trials should be conducted with low risk of bias, low risk of design errors, and low risk of random errors. Future trials ought to focus their assessments on patient-centred clinical outcomes.
- WHO recommend that additional studies are needed on life-long effectiveness and on the need for booster doses in different subgroups. Additional long-term studies are needed to explore lifelong protection conferred by hepatitis B vaccine and the need for booster doses in different subgroups of the population, particularly in HIV-infected/HIV-exposed infants.
- Many interventions (for alcohol, obesity and hepatitis) are of short duration, with little or no follow-up. Longer term follow-up is necessary (or modelling over the long term e.g. 20 years+) to see the full impact of population or community level interventions. NICE recommend at least a 12 month post intervention follow-up for obesity research studies. Modelling studies provide a cost-efficient way of testing the longer term impact of interventions to prevent obesity, for example Ahern *et al's* (2017) study.[155]. Modelling studies offer an alternative, as they provide the ability to test the most effective intervention, or suite of interventions with a combined effect, over the long term, in any specified population. Modelling the cost-effectiveness of public health interventions for non-communicable diseases such as liver disease is an expanding academic field that is starting to embrace more sophisticated modelling structures[218], including microsimulation models, which are among the most flexible options for modelling chronic diseases.

CONCLUSIONS

The epidemiological burden of liver disease

Data on the current and historical prevalence and mortality from published sources and international databases suggest that liver disease is a sizeable and increasingly important public health problem in European countries. Some parts of Europe are estimated to have more than 1100 prevalent cases of cirrhosis and other chronic liver disease per 100,000. European mortality data indicates that on average two thirds of liver disease mortality occurs in individuals below the age of 65 years. Alcohol is a large contributor to liver disease mortality rates across Eastern, Central and Northern Europe. Liver cancer also represents a large proportion of deaths for the majority of countries, while deaths due to viral hepatitis are concentrated in Southern Europe. NAFLD/NASH, autoimmune and metabolic and miscellaneous liver disease all represent smaller proportions of the overall burden of liver disease in Europe.

One of the important limitations of studying the epidemiological burden of liver disease is the availability and quality of data. Public health depends on reliable information about causes of mortality, to be able to effectively respond to changes. In many countries however, the coding of deaths was not granular or sufficiently specific to accurately establish proper aetiology (as the current mortality is coded in the WHO mortality database, it is sufficient to separate cirrhosis and cancer and a few other rarer diseases but not enough to properly investigate aetiology).

Although most countries with statistical systems for cause of death now use the ICD classification for coding, not all countries have introduced the international standard certificate for reporting cause of death. Furthermore, physicians often do not receive adequate training in standard ICD death certification practices. Rampatige *et al.*(2014) proposed a framework for conducting medical record reviews.[219] They suggest such studies be undertaken specifically in liver disease deaths to assess whether deaths from liver disease are being reliably recorded in hospital settings. Cause of death statistics of poor quality have limited policy utility and may even seriously mislead policy debates.[219] Another alternative for the analysis of the burden of liver disease is to use country-specific data, which may be coded differently to that provided to the WHO. However, this option is limited as it would not allow between country comparability of epidemiological trends.

The need to compare and contrast countries liver disease burden also motivated the use of modelled GBD prevalence data, despite the existence of country-specific estimates. Modelled prevalence data indicated a consistent increase in the rate of cirrhosis and liver cancer in the population for almost all countries over the past decades, with the rates of increase varying between countries. The results from this source are dependent on the model used, definitions of outcomes, as well as selection of the input data, and so trends in liver disease prevalence should be analysed with caution. The wide geographic variation in the availability of high-quality cause of death and cancer registry data are reflected in the uncertainty associated with the GBD estimates.[220]

Of note is that the Global Burden of Disease data used was released in 2016. The current and historical estimates for prevalence of cirrhosis and other chronic liver diseases were up to 12 times higher than those released in the 2015 edition of the GBD in large part due to the fact that for the first time in 2016, compensated and decompensated cirrhosis was modelled,

while only decompensated liver disease prevalence had been estimated in previous work. One limitation of the GBD prevalence data is that it only provides four causes of liver disease: due to alcohol use, due to hepatitis B infection, due to hepatitis C infection and due to other causes. It is not currently possible to separate out cases due to fatty liver disease, an increasingly important aetiology for liver disease in Europe. This is perhaps one of the larger data gaps for estimation of the liver disease burden in Europe, along with accurate information on alcohol-related liver disease prevalence. In addition, the four causes may vary in the bias they are likely to represent: the etiological attribution of the liver cancer burden, hepatitis B and hepatitis C related cases are less prone to misclassification based on the use of objective laboratory assessments, in contrast to self-reported data for alcohol use.[220] For future iterations of the GBD, inclusion of additional aetiologies as well as estimating the burden of cholangiocarcinoma and hepatocellular carcinoma separately should be considered.

Prevalence data for hepatitis B and C chronic infections in both the general population and high risk groups was sparse, and methods used to derive this varied greatly by country and setting. Trend analyses indicated that the prevalence of both chronic infections was decreasing over time for almost all countries, except for some notable exceptions with specific contexts, such as immigration and removal of policies that reduce drug use harm. There is a clear need for standardised surveys and further research into ways to take into account the clustering of prevalence among specific risk groups in any prevalence study. Some modelling had been undertaken in hepatitis epidemiology, in order to fill in the gaps when data were not available. However the estimates from these models are limited both by the conceptual structure of the models, the assumptions made, as well as the quality of the original input data itself, as mentioned above.

The availability and quality of current and historical epidemiological data on the burden of liver disease is limited, but does provide some insights into the needs for future control. Public health policy for liver disease would however be greatly supported by information on the future trends in liver disease. This would help with policy and resource prioritisation and inform on the geographic and demographic focusses of the next 20 or more years. One method for estimating potential trends in future incidence and prevalence of disease would be to model the future in the upstream risk factors, as they, along with changes in demographics and future interventions and treatments are likely to have the greatest impact on epidemiology.

Data on the mortality, but also the prevalence and incidence of disease could be improved across Europe, including standardising the reporting and collecting of epidemiological data. Developing scores to monitor and evaluate data systems could be future work in this area.

The modifiable risk factor for liver disease

The available data on the determinant behavioural risk factors for liver disease were analysed from a range of sources.

Information on alcohol consumption shows geographical variation in the patterns of consumption across Europe. While consumption has decreased dramatically from very high levels in some countries, in others there have been large increases in consumption. Looking at alcohol intake only in terms of total litres consumed can only provide a part of the picture however, and consideration must be given to the types of alcohol (beer, wine or spirits)

consumed as well as the patterns of alcohol consumption, in particular focussing on the extreme levels of consumption where most of the health risks and harms are concentrated.

Epidemiological data on NAFLD/NASH was very limited: few deaths were recorded from fatty liver disease, except in countries with established obesity epidemics. Prevalence data was not modelled for liver disease due to excess adiposity as this was combined in the other causes category. However, evidence from prevalence studies of obesity in adults, as well as knowledge about the dose-response relationship between BMI and risk of liver disease (NAFLD as well as liver cancer) firmly indicate that the high (and mainly increasing) adult and child obesity prevalence in European countries will play an important role in the future burden of liver disease.

When considering the impact of the modifiable, largely behavioural risk factors for liver disease (which include alcohol consumption, excess adiposity, using obesity as a proxy, and behaviours such as injection drug use), further attention will need to be given to how these behaviours interact and how the multi-risk behaviour will impact on the burden of liver disease. Another important feature of risk factors for liver disease is that the majority of the risk is concentrated at the extremes of the distribution of population behaviours (individuals who consume large amounts of alcohol, individuals with high BMI, in particular morbid obesity, and hard to reach high-risk groups for injection drug use. The distribution and impact of these sub groups are often difficult to assess using population-level data, yet these are the populations most likely to be impacted by risk reduction policies.

Policies and interventions aimed at reducing the risk factors for liver disease

While countries have a varied picture of liver disease, there is an increasing shift away from viral causes to behavioural causes such as alcohol consumption and obesity. The epidemiological data and information on the upstream risk factors indicate that the burden of liver disease across Europe is likely to increase in future years.

Governments, policy makers and public health agencies should implement established effective interventions, which include:

- Minimum unit pricing to reduce alcohol consumption, in particular in the heaviest drinkers. The likely impact of this policy is to reduce health inequalities, by reducing harmful consumption more in those of lower socioeconomic status
- Introduction of a 20% tax on sugar-sweetened beverages to reduce obesity
- Restriction of marketing of alcohol and unhealthy foods, coupled with food reformulation to reduce the fat and sugar content of the most harmful food commodities.

Within the medical field, further efforts can be developed, in priority to:

- Identify the population with undiagnosed NAFLD and Hepatitis C infection (the “rest of the iceberg”)
- Strengthen specialised liver services, and develop collaboration with other disciplines (addiction, weight management, as well as traditional infection disease specialisms)
- Promote immunisation with hepatitis B vaccine to high risk groups as well as maintaining the universal neonatal vaccination schedule and rolling out the treatment of hepatitis C infection with antiretroviral, in particular the new class of DAAs.

While policy priorities have been identified and can be introduced, the evidence base could be further supported by additional research into the field of liver disease prevention.

Standardised, timely, accurate and relevant epidemiological data on diseases and their risk factors would greatly help to support and evaluate public health efforts. While the effectiveness of many interventions have been evaluated, this was often done in narrow studies with specific contexts, which should be expanded to other countries/regions. In particular, data on the impact of interventions on health inequalities, and the cost-benefit, along with simply the effectiveness of a policy should be evaluated. Where long term randomised control trials are not feasible, this information is likely to come from epidemiological and economic modelling studies.

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SUPPLEMENTARY MATERIAL

Supplementary material for Part 1

Table 9. Sources of epidemiological data on liver disease

Epidemiological measure	Source	URL / location	Notes
Mortality	World Health Organization European Detailed Mortality Database(EMDB) raw data & World Health Organization Health For All database (long term tends)	http://www.who.int/healthinfo/statistics/mortality_rawdata/en/ https://gateway.euro.who.int/en/hfa-explorer/	Data on all ICD-10 codes were extracted from the EMDB and recoded according to recommendations into nine broad liver disease categories
Prevalence	Global Burden of Disease (GBD) results from 2016 release: Global Health Data Exchange tool	http://ghdx.healthdata.org/gbd-results-tool	Note, for the first time, compensated and decompensated chronic liver disease and cirrhosis were modelled by GBD, when only decompensated disease was modelled in previous version of the GBD.
Incidence of hepatitis B and C	Grey and published literature, including ECDC reports and WHO-sponsored systematic reviews ; modelled data requested from the Polaris Observatory was also used for comparison	https://ecdc.europa.eu/en/viral-hepatitis Polaris observatory data: The CDA Foundation. Lafayette, CO: CDA Foundation, 2017. Available from http://polarisobservatory.org/	
Transplantation	European Liver Transplant Registry	http://www.eltr.org/	Data was requested from the ELTR and kindle prepared by Vincent Karam and René Adam
Population data	United Nations DESA/Population Division World Population Prospects 2017	https://esa.un.org/unpd/wpp/Download/Standard/Population/	

1. WHO mortality coding methodology

The WHO Mortality Data is collected from national vital registration systems where deaths have been medically certified and registered with an underlying cause, defined as “the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury”, and where these have been coded according to the International Classification of Diseases (ICD). The competent authorities of each Member State transmit population data and mortality data to the WHO for the population covered by the death registration system – this may not be for the whole country, and the data are labelled accordingly where this is the case. The WHO states that completeness of death registration “may be less than 100% for the specified registration population”. Where death registration is less than 100% for the specified

population, the WHO estimates the completeness in order to calculate death rates. The demographic techniques used to do this are unclear.

Where the death registration system does not cover the national population, the coverage is calculated as the total deaths reported divided by the total estimated deaths in the national population, in the same year.

The WHO also validates estimated deaths by cause taking into account that different countries may use different coding practices, particularly when it comes to poorly-defined conditions and unknown causes. It is not clear how this estimation is done, but they do state that if deaths are coded with non-official codes then they are replaced with the official code that is deemed most appropriate.

2. Recoding raw mortality data

In order to better represent the aetiology of liver disease mortality, ICD-10 four digit codes were recoded into nine liver disease categories, as shown in Table 10. ICD-10 definitions were obtained from the International Statistical Classification of Diseases and Related Health Problems 10th Revision http://apps.who.int/classifications/icd10/browse/2010/en#/E11. It was not possible to use the WHO mortality data recoded with ICD-9 as this was only available in the basic tabulation form, with no raw ICD-9 four-digit data downloadable.

Raw data on deaths by age, sex and cause (ICD-10 code) were merged to historical UN population data by age group and sex to obtain mortality rates per 100,000 population. Deaths, potential years of life lost (PYLL) and potential working years of life lost (PWYLL) rates per 100,000 were calculated using country, year, age and sex specific population estimates.

Table 10. Recoding mapping for liver disease ICD-10 codes

Mortality recode category	ICD-10 4-digit code	ICD-10 Definition
Viral hepatitis	B15.0-B19.9	B15-B19 Viral hepatitis
Cancer	C22.0-C22.9	C22 Malignant neoplasm of liver and intrahepatic bile ducts
Alcoholic	K70.0-K70.9	K70 Alcoholic liver disease
Auto Immune	K73.0-K73.9	K73 Chronic hepatitis, not elsewhere classified
	K74.3	K74.3 Primary biliary cirrhosis
	K74.5	K74.5 Biliary cirrhosis, unspecified
	K75.3-K75.4	K75.3 Granulomatous hepatitis, not elsewhere classified ; K75.4 Autoimmune hepatitis
Metabolic	E83.0	E83.0 Disorders of copper metabolism
	E83.1	E83.1 Disorders of iron metabolism
NAFLD/NASH	K75.8	K75.8 Other specified inflammatory liver diseases
	K76.0	K76.0 Fatty (change of) liver, not elsewhere classified
Miscellaneous	K71.0-K71.9	K71 Toxic liver disease
	K74.4	K74.4 Secondary biliary cirrhosis
	K75.0-K75.2	K75.0 Abscess of liver ; K75.1 Phlebitis of portal vein ; K75.2 Nonspecific reactive hepatitis
	K76.1-K76.5	K76.1 Chronic passive congestion of liver ; K76.2 Central haemorrhagic necrosis of liver ; K76.3 Infarction of liver ; K76.4 Peliosis hepatitis; K76.5 Hepatic veno-occlusive disease
	K76.8	K76.8 Other specified diseases of liver
	K77.0-K77.9	K77 Liver disorders in diseases classified elsewhere
Unknown	K72.0-K72.9	K72.0 Acute and subacute hepatic failure ; K72.1 Chronic hepatic failure; K72.9 Hepatic failure, unspecified
	K74.6	K74.6 Other and unspecified cirrhosis of liver

	K76.6-K76.7	K76.6 Portal hypertension ; K76.7 Hepatorenal syndrome
	K74.0-K74.2	K74.0 Hepatic fibrosis; K74.1 Hepatic sclerosis ; K74.2 Hepatic fibrosis with hepatic sclerosis
	K75.9	K75.9 Inflammatory liver disease, unspecified
	K76.9	K76.9 Liver disease, unspecified
	I85.0-I85.9	I85 Oesophageal varices
	I81; I82.0	I81 Portal vein thrombosis ; I82.0 Budd-Chiari syndrome
	I98.2-I98.3, I68.4,	I98.2 Oesophageal varices without bleeding in diseases classified elsewhere ; I98.3 Oesophageal varices with bleeding in diseases classified elsewhere ;

3. Calculation of PYLL and PWYLL from mortality data

Total deaths in each sex and fiver- year age group were converted to PYLL by multiplying by the difference between the midpoint of the age group and the life expectancy of 75 years, according to the methods from WHO Deaths above the age of 75 years did therefore not contribute to PYLL. The same principle was applied when calculating PWYLL: all deaths before the age of 15 years represented a full 50 years of working life lost; from 15 onwards, the total potential working years of life lost were represented by the difference between the midpoint of the age group and 64 years. Beyond 64 years, deaths did not contribute to total PWYLL. Example: 1 death in a person in the age group 45-49 years would lead to 75 - 47.5 = 27.5 PYLL and to 64-47.5= 16.5 PWYLL.

4. Age-standardisation of mortality data for both genders

Death counts were available by sex and five year age bands. An aggregate ‘all ages’ variable was created for each sex and for both genders combined. In order to allow more precise comparisons of death rates between countries however, mortality data for both genders was age-standardised using the World Health Organization's (WHO) new World Standard Population, http://www.who.int/healthinfo/paper31.pdf and http://apps.who.int/healthinfo/statistics/mortality/whodpms/definitions/pop.htm As in the WHO’s own methodology for estimation of mortality rates, no adjustment is made to the mortality data based on the coverage.

5. Calculation of rates

Mortality, PYLL and PWYLL rates per 100,000 population were calculated using country, year, age and sex specific population estimates from the UN population Division.

6. GBD data

The GBD study describes mortality and morbidity trends from major diseases, injuries and risk factors to health at global, national and regional levels from 1990 to the present, allowing comparisons across populations and over time. Data on cirrhosis of the liver and other chronic liver diseases, and liver cancer were downloaded from the GBD Results tool, for 1990 to 2016. For the first time in 2016, GBD added the MarketScan database to the

input data when modelling prevalence and modelled compensated cirrhosis for the first time. GBD models decompensated cirrhosis, defined by cirrhosis (or a closely related diagnosis code) as the primary diagnosis in hospital data and total cirrhosis (compensated plus decompensated) when cirrhosis is a secondary diagnosis in hospital data. This includes ICD1-0 codes K70-K77, I85, P78.81.

Cases were attributed to hepatitis B, hepatitis C, alcohol, and other causes, which include remaining aetiologies like liver flukes, NASH, and aflatoxins. To estimate proportions for all locations, by sex, and over time, models were generated using DisMod-MR 2.1, a Bayesian meta-regression model. Liver cancer mortality estimates were split into aetiologies using the modelled proportions

For further information, see page 330 to 333 of the supplementary appendix 1 of the GBD 2016 Capstone paper.[221]

7. Literature review protocol

A comprehensive review of the published and grey literature was performed, according to the following protocol:

Peer reviewed literature sources searched included PubMed: reviews and meta-analyses articles. The grey literature sources searched include Google, and national public health websites.

Table 11. Example of the search strategy used:

Disease terms	Epidemiological terms	Countries
Liver disease Liver disorder Liver dysfunction Hepatic disease Hepatic disorder Hepatic dysfunction	Incidence OR prevalence Data OR epidemiology OR statistic* Statistics and numerical data (Topic)	Austria* OR Belg* OR Bulgari* OR Croati* OR Cypr* OR Czec* OR Denmark OR Danish OR Estoni* OR Finland OR Finnish OR France OR French OR German* OR Greece OR Greek OR Hungar* OR Ireland OR Irish OR Ital* OR Latvia* OR Lithuani* OR Luxembour* OR Malta OR Maltese OR Netherlands OR Dutch OR Poland OR Polish OR Portug* OR Romani* OR Slovaki* OR Sloveni* OR Spain OR Spanish OR Swed* OR United Kingdom OR United Kingdom OR Engl* OR Wales OR Welsh OR Scotland OR Scottish OR Northern Ireland OR Uzbekistan OR Russia OR Kazakhstan OR Norw* OR Iceland* And regional terms where possible, e.g. Eastern Europe, Europe, EEA, Balkans etc.

Eligibility criteria included reviews presenting relevant mortality, prevalence, incidence survival and years of life lost data for Liver conditions and outcomes listed below in the general population (no age restrictions) for any of the 35 HEPAHEALTH countries. Data eligible for inclusion should be presented in rates per 100,000, or provides data to enable conversion to rate per 100,000. (I.e. both numerator and denominator are reported together, other rates are reported such as per 1000). No language restrictions were applied

(translation of non-English publications will be performed where possible; any exclusions will be documented). Mortality data sources were included if they presented up to 30 years historical data, while for other metrics, data was included on the last 10 years of data available. Data presented disaggregated by sex, age, and other socioeconomic data if available, in particular for the latest available data point (as this will be used in the later modelling project).

Literature was excluded if they provided data on conditions with generally short-term/acute with good recovery rates, or are relatively rare compared to the included conditions, such as pregnancy-related liver disease as acute liver diseases, gallstones, drug-induced acute liver damage

Measures such as QALYs, EQ-5D or other utility values were not be extracted, but their presence within a database or journal article was noted in the mapping and data extraction documents. Hospital-based measures, such as inpatient stays due to liver problems and number of bed days used were also excluded due to time constraints. Data based on special groups within a population, e.g. injection drug users, were not included in the data extraction.

Included literature was graded according to the GRADE approach.

Data extraction was performed using a form in MS Excel, using the following header list:

Table 12. Data extraction header list

Reference id	**Liver disease outcome**	**Age group**
URL	Aetiology category	Sex
Author	Year data collected	Ethnicity
Year of publication	Sampling approach	Statistical analysis method
Region	Secondary data analysis	Epidemiological measure
Country	Original data source if secondary	Metric/unit
Urban/Rural	Sample size	Key results
	General population	

8. Time trends in mortality from intrahepatic cholangiocarcinoma (C22.1)

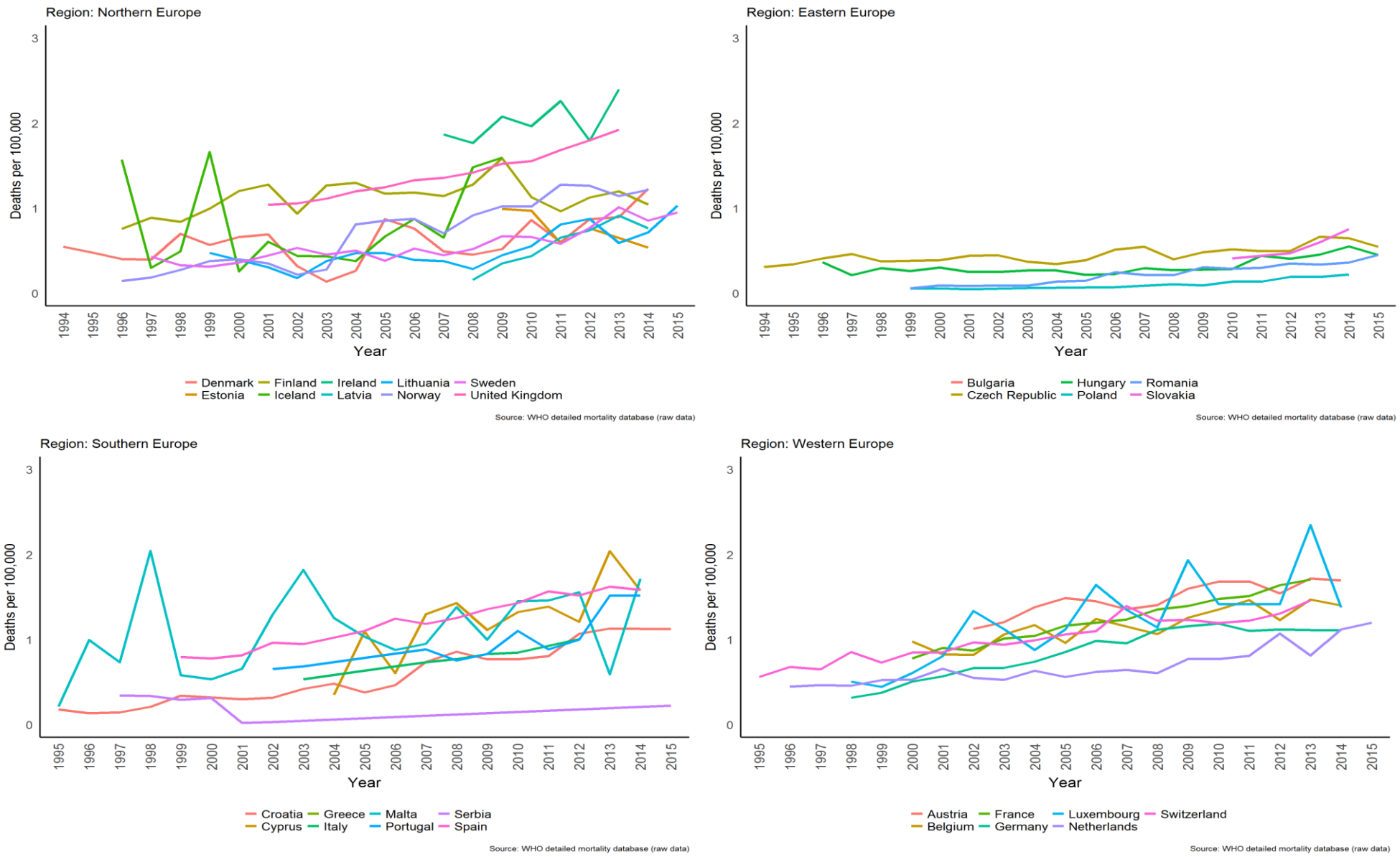


Figure 78. Time trends in age-standardised mortality from intrahepatic cholangiocarcinoma (C22.1) - both genders by region

9. Time trends in Hepatitis B and C prevalence using Polaris Foundation data

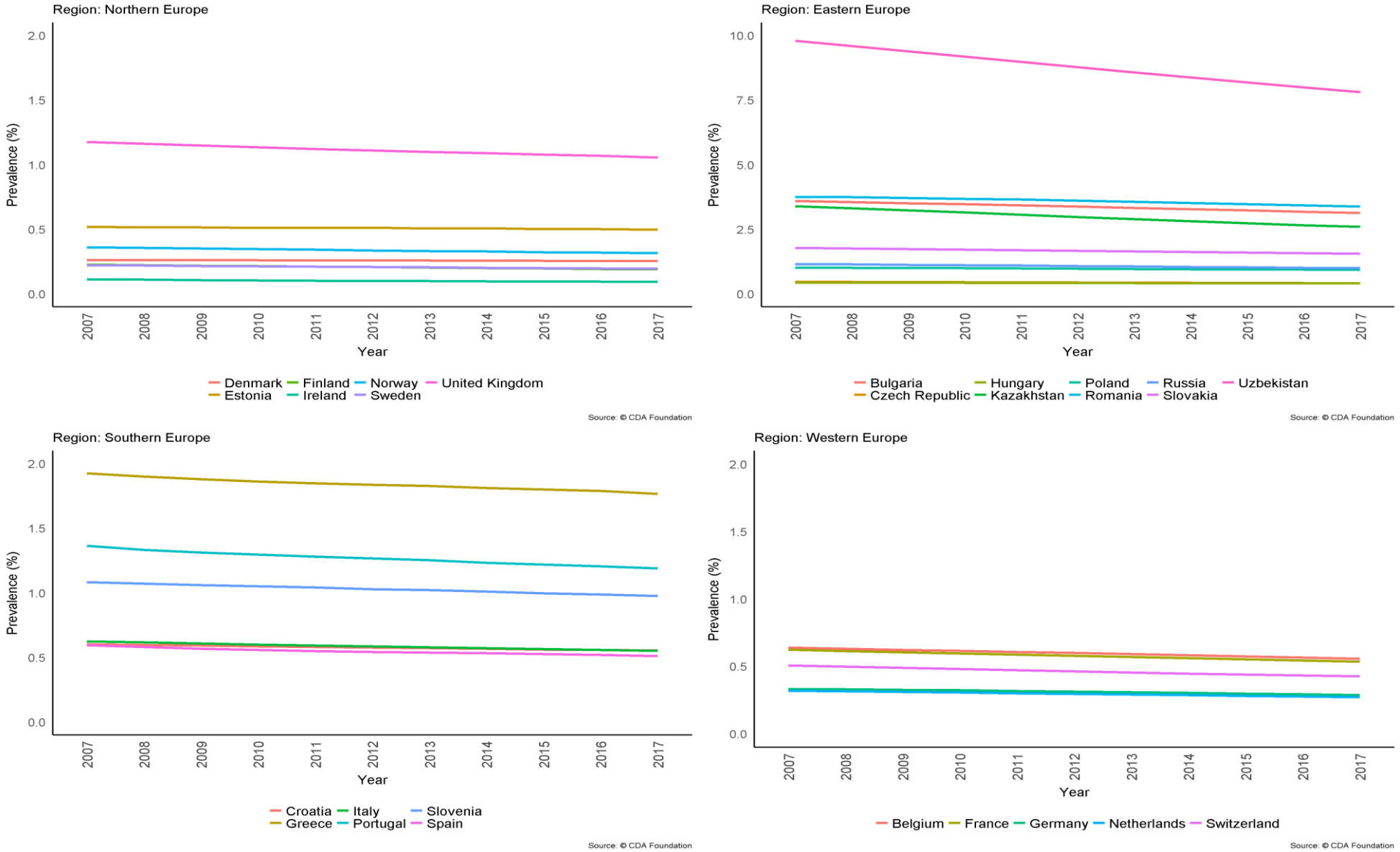


Figure 79. Hepatitis B prevalence from HBsAg over time estimated by the Polaris Observatory (males and females) – modelled data

Data for Cyprus, Iceland, Latvia, Lithuania, Luxembourg, Malta and Serbia not available.

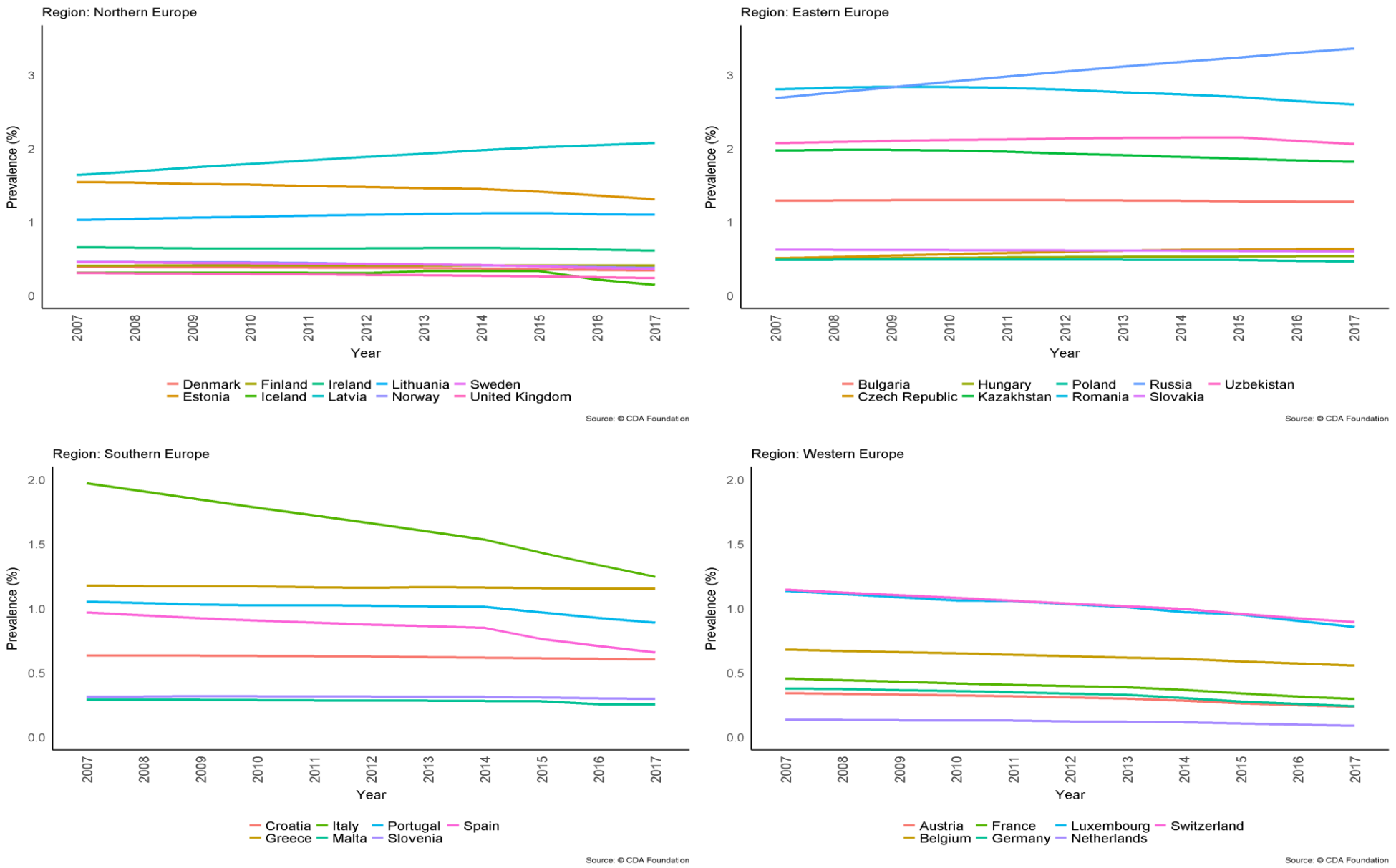


Figure 80. Hepatitis C prevalence from hepatitis C viremic cases over time estimated by the Polaris Observatory (males and females) – modelled data

Data for Cyprus and Serbia not available.

10. European liver transplant registry data

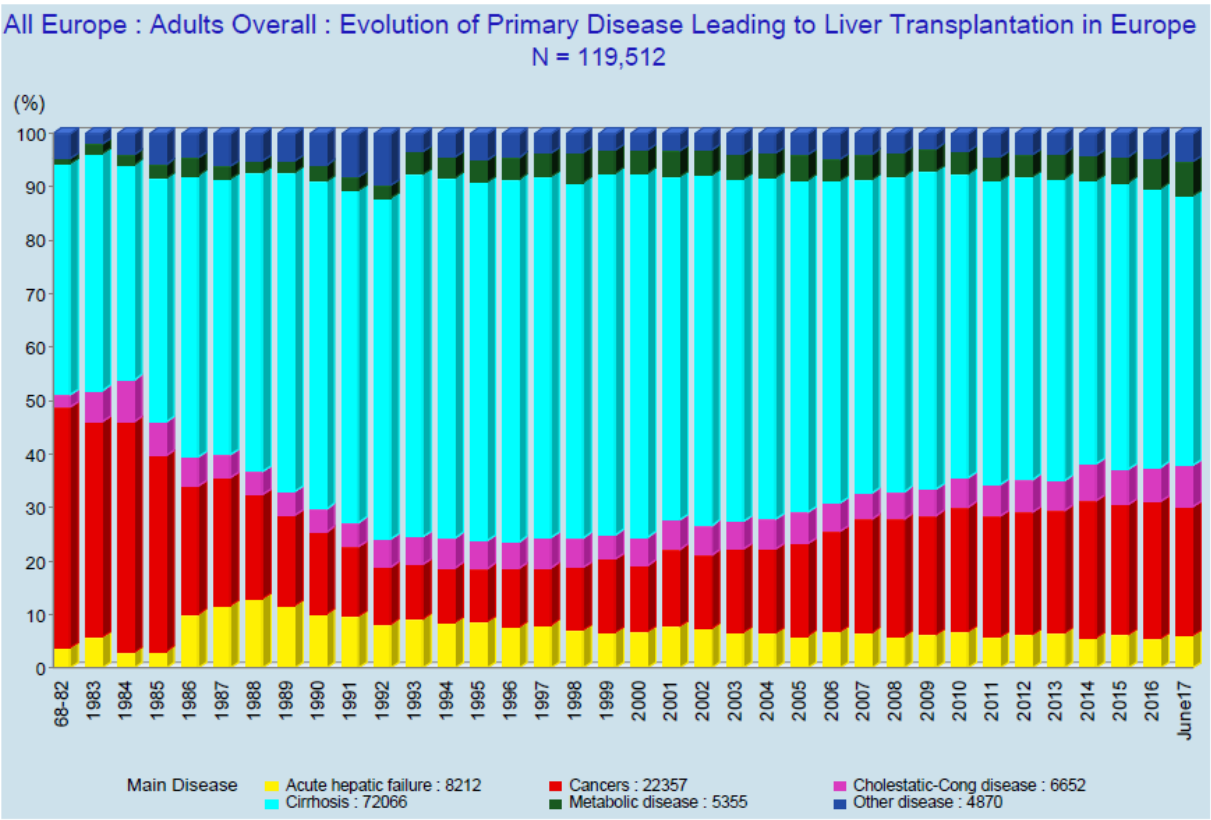


Figure 81. Evolution of Primary Disease Leading to Liver Transplantation in Europe (1968-2017)

Supplementary material for Part 2

Table 13. Sources of liver disease risk factor data

Risk factor	Source	URL / location	Notes
Alcohol	World Health Organisation Health for All database	https://gateway.euro.who.int/en/hfa-explorer/	
Diabetes	International Diabetes Federation (IDF) Diabetes Atlas 2000, 2003, 2007, 2010, 2011, 2013, 2015	http://www.diabetesatlas.org/resources/previous-editions.html . Personal communication with IDF diabetes Atlas team to obtain age-specific diabetes data for 2007 onwards.	Data provided combines Type 1 and type 2 diabetes, as recommended by personal communication with members of IDF, 90% of the total diabetes prevalence was used to represent type 2 diabetes alone. In 2011, the IDF revised the methodology for generating estimates of diabetes prevalence. Drawing on expert opinion in a systematic, explicit, and adaptable way to select data sources, the new methods preferentially select data sources that are nationally representative over non-national data, use pooled sources only if high quality data was insufficient and studies conducted using the 2-hour oral glucose tolerance test were preferentially selected based on the judgment of the expert panel. The new methods are a departure from the previous IDF methodology that did not apply a weighting to included data sources and was therefore more susceptible to bias.
Injecting drug use	European Monitoring Centre for Drugs and Drug Addiction (2017) European Drug Report 2015: trends and Development; Publication Office of the European Union, Luxembourg	http://www.emcdda.europa.eu/edr2017_en	
Obesity -	EHIS data for 2014. And country-specific sources, see table below		United Kingdom data used England data as proxy. EHIS 2014 used to represent most recent year of data – when country=specific data was available for 2014 (e.g. Estonia, Finland, Romania, the United Kingdom and Russia), EHIS data was not included. Personal communication data was used in the plots and graphs produced, but were not provided as part of the databases created for the project.

Table 14. Obesity prevalence sources from self-reported national samples

Country	Study name reference (* measured; ** both measured and self-reported; personal communications in italics)	Data Years	Sample size		Age groups (years)
			M	F	
Austria	Health Statistics Austria, 2002	1999	3368	3624	15-100
	Schwarz, Abdominal Obesity and Cardiometabolic Risk Factors in Austria, 2007	2006	528	526	30-74
	Klimont et al, Österreichische Gesundheitsbefragung, 2006/2007	2007	2914	3203	20-100
Belgium	Belgian Health Interview Survey, 1997	1997	3934	4137	15-100
	Belgian Health Interview Survey, 2001	2001	4582	4809	15-100
	Belgian Health Interview Survey, 2004	2004	4836	5483	15-100

	Belgian Health Interview Survey, 2008	2008	4093	4738	15-100
	Belgian Health Interview Survey, 2013	2013	4111	4515	18-75+
Bulgaria	WHO; Survey of the Health Status of the Population	2001	8008		25-74
	WHO; Petrova et al 2006	2004	515	516	25-74
	National behavioral risk factor survey among population aged 25-64, 2007 (CINDI)	2007	-		25-74
	Eurostat database: Health Interview Survey 2008 Bulgaria	2008	5664		25-84
	International Social Survey Programme: Health and Health Care - ISSP 2011 *	2011	422	581	20+
Croatia	WHO; Budak, 2003 *	1998 (1997-1999)	1967	2982	0-100
	WHO; Croatian Adult Health Survey *	2003	2878	6162	18+
	International Social Survey Programme: Health and Health Care - ISSP 2011*	2011	575	635	20+
Cyprus	*Statistical Service Cyprus, personal communication*	*2003*	*267866*	*284397*	*15-100*
	Statistical Service Cyprus, personal communication	*2008*	*277077*	*300761*	*15-100*
Czech Republic	WHO; Sample Survey of the Health Status of the Czech Population HIS CR 1993	1993	734	833	20-74
	WHO; Sample Survey of the Health Status of the Czech Population 1996	1996	1031	1123	20-74
	WHO; Sample Survey of the Health Status of the Czech Population HIS 1999	1999	1603	1760	20-74
	WHO; Sample Survey of the Health Status of the Czech Population HIS 2002	2002	1142	1284	20-74
	Eurostat database: European Health Interview Survey 2008 Czech Republic	2008	940	1015	20-74
Denmark	SUSY 2000, National Institute of Public Health	2000	8126	8275	16-100
	Ekholm et al, Health and mortality survey Denmark, 2005	2006	7046	7441	16-100
	SUSY 2010, National Institute of Public Health	2010	79347	92873	16-100
Estonia	*Unpublished data obtained from Mare Tekkel*	*1998*	*561*	*743*	*16-64*
	Kasmel et al. Health behaviour among Estonian adult population, spring 2000	2000	547	790	16-64
	Kasmel et al. Health behaviour among Estonian adult population, spring 2002	2002	542	779	16-64
	Tervise Arengu Instituut, Health behaviour among Estonian adult population	2004	1299	1743	16-64
	Tekkel et al. Health Behavior among Estonian Adult Population, 2006	2006	1112	1706	16-64
	Tekkel et al. Health Behavior among Estonian Adult Population, 2008	2008	1248	1702	16-64
	Tekkel and Veideman, Health Behaviour among Estonian Adult Population 2010	2010	1227	1760	16-64
	Tekkel and Veideman, Health Behaviour among Estonian Adult Population 2012	2012	1235	2916	16-64
	Tekkel and Veideman, Health Behaviour among Estonian Adult Population 2014	2014	1013	1525	16-64
Finland	WHO; Raitarki et al, Distribution and determinants of serum high-sensitive C-reactive protein	2001	1026	1193	20-39
	WHO; Helakorpi et al, Health behaviour among Finnish adult population, 2002	2002	1462	1757	15-64
	WHO ; Helakorpi et al, Health behaviour among Finnish adult population, 2003	2003	1516	1819	15-64
	WHO; Helakorpi et al, Health behaviour among Finnish adult population, 2004	2004	1520	1805	15-64

	WHO; Helakorpi et al, Health behaviour among Finnish adult population, 2005	2005	1500	1727	15-64
	WHO; Helakorpi et al, Health behaviour among Finnish adult population, 2006	2006	1450	1761	15-64
	WHO; Helakorpi et al, Health behaviour among Finnish adult population, 2007	2007	1397	1789	15-64
	WHO; Helakorpi et al, Health behaviour among Finnish adult population, 2008	2008	1346	1776	15-64
	Helakorpi et al, Health behaviour among Finnish adult population, 2009	2009	1240	1620	15-64
	Helakorpi et al, Health behaviour among Finnish adult population, 2010	2010	1221	1539	15-64
	Helakorpi et al, Health behaviour among Finnish adult population, 2011	2011	1181	1565	15-64
	Helakorpi et al, Health behaviour among Finnish adult population, 2012	2012	1093	1456	15-64
	Helakorpi et al, Health behaviour among Finnish adult population, 2013	2013	1080	1411	15-64
	Helakorpi et al, Health behaviour among Finnish adult population, 2014	2014	1109	1469	15-64
France	Maillard et al, Trends in the prevalence of obesity in the French adult population, 1999	1992	7250	7856	18-100
	Enquête épidémiologique nationale sur le surpoids et l'obésité, Roche 2009	1997	-	-	18-100
	Enquête épidémiologique nationale sur le surpoids et l'obésité, Roche 2009	2000	-	-	18-100
	Enquête épidémiologique nationale sur le surpoids et l'obésité, Roche 2009	2003	25770		18-100
	Enquête épidémiologique nationale sur le surpoids et l'obésité, Roche 2009	2006	-	-	18-100
	Enquête épidémiologique nationale sur le surpoids et l'obésité, Roche 2009	2009	-	-	18-100
	Enquête épidémiologique nationale sur le surpoids et l'obésité, Roche 2012	2012	12214	13500	18-100
Germany	WHO; Hoffmester et al, National trends in risk factors for CVD in Germany, 1994*	1991	2556	2715	25-69
	Microzensus 1999, Federal Statistics Office, personal communication	*1999*	*24513*	*25765*	*18-100*
	Microzensus 2003, Federal Statistics Office, personal communication	*2003*	*24222*	*25235*	*18-100*
	Microzensus 2005, Federal Statistics Office, personal communication	*2005*	*25873*	*26654*	*18-100*
	Nationale Verzehrs Studie II 2008, personal communication	*2008*	*6117*	*7090*	*18-80*
	Microzensus 2009, Federal Statistics Office, personal communication	*2009*	*25112*	*25560*	*18-100*
	German Health Interview and Examination Survey for Adults (DEGS) "Studie zur Gesundheit Erwachsener in Deutschland" *	2008/2012	3790	4198	18-79
	Microzensus 2013,Health Questions Federal Statistics Office,	2013	23508	23589	18-75+
Greece	*Survey on Income and Living Conditions, Hellenic Statistical Authority, personal communication*	*1998*	*4659710*	*5133801*	*15-100*
	Survey on Income and Living Conditions, Hellenic Statistical Authority, personal communication	*1999*	*4428897*	*4912742*	*15-100*
	Survey on Income and Living Conditions, Hellenic Statistical Authority, personal communication	*2000*	*4398975*	*4831754*	*15-100*
	Survey on Income and Living Conditions, Hellenic Statistical Authority, personal communication	*2001*	*4360600*	*4867626*	*15-100*
	WHO; Kapantais et al, 2004	2003	8234	9107	20-69
	Hellas Health I Survey Personal communication Filippo	*2006*	*459*	*506*	*18+*

	Fillipidis				
	Hellas Health II Survey Personal communication Filippo Fillipidis	*2008*	*683*	*763*	*18+*
	Survey on Income and Living Conditions, Hellenic Statistical Authority, personal communication	*2009*	*4369422*	*4618038*	*15-100*
	Hellas Health III Survey, Personal communication Filippo Fillipidis	*2010*	*492*	*487*	*18+*
Hungary	WHO: Boros et al. National Health Interview Survey 2003	2003	2214	2741	25-64
	Eurostat database: Health Interview Survey 2008 Hungary	2009	5051		25-64
Iceland	*Personal communication E. Gisladottir*	*1990*	*557*	*577*	*15-80*
	Personal communication E. Gisladottir	*2002*	*591*	*656*	*18-79*
	Personal communication E. Gisladottir	*2007*	*2670*	*2995*	*18-79*
	Personal communication E. Gisladottir	*2010*	*621*	*640*	*18-79*
	Survey of Icelandic Diet 2010/2011	2010/2011	625	646	18-80
Ireland	north/south Ireland Food Consumption Survey (NSIFCS)	1998	2688	3074	18-64
	Survey of Lifestyle, Attitudes and Nutrition in Ireland (SLAN)	2002	2164	3149	18-100
	Survey of Lifestyle, Attitudes and Nutrition in Ireland (SLAN) *	2007	942	1224	18-100
	Growing Up in Ireland (GUI)*	2008	6761	7799	18-100
	Combined NANS and GUI data*	2009	8389	8415	18-100
	north/south Ireland Food Consumption Survey (NSIFCS)*	2010	361	375	18-100
	National Adult Nutrition Survey 2011*	2011 (2008/2010	740	760	18-90
Italy	*Calza et al, Obesity and prevalence of chronic diseases, personal communication*	*2000*	*55303*	*59716*	*18-100*
	WHO; Istituto Nazionale Di Statistica. Stili di vita e condizioni di salute, 2004	2002	21851	23738	18-100
	WHO; Istituto Nazionale Di Statistica. Stili di vita e condizioni di salute, 2004	2003	21233	23151	18-100
	WHO; Gallus et al, Overweight and obesity in Italian adults, 2004	2004	1407	1525	18-100
	WHO; Istituto Nazionale Di Statistica. Health conditions and risk factors, 2007	2005	19384	21165	18-100
	Istituto Nazionale Di Statistica . La vita quotidiana nel 2006, personal communication	*2006*	*19378*	*21169*	*18-100*
	Istat database, personal communication	*2007*	*19187*	*20822*	*25-100*
	Istat database, personal communication	*2008*	*23522*	*25437*	*18-100*
	Istat database, personal communication	*2009*	*23689*	*25592*	*18-100*
	Istat database, personal communication	*2010*	*19151*	*21060*	*25-100*
	Istat database "Aspetti della viota quotidiana" Anno 2013	2013	50000		
Kazakhstan	WHO: Demographic and Health Survey*	1999	-	2238	15-49
	Personal communication B. Roberts	*2001*	*802*	*986*	*18-60+*
	Personal communication B. Roberts	*2010*	*851*	*939*	*18-60+*
	*Personal communication S. Tazhybayev**	*2012*	*1299*	*2430*	*15-65+*
Latvia	Pudule et al. Health behaviour among Latvian adult population, 2002	2002	856	1091	15-64
	Unpublished data obtained from Dace Krievkalne	2003	3189	3647	20-74
	Pudule et al. Health behaviour among Latvian adult population, 2004	2004	742	1014	15-74
	Pudule et al. Health behaviour among Latvian adult	2006	665	873	15-74

	population, 2006				
	Eurostat database: European Health Interview Survey 2008 Latvia	2008	2867	3591	18-94
	Centre for Disease Prevention and Control	2012	1340	1631	15-64
Lithuania	WHO; Grabauskas et al, 2000	2000	989	1183	20-64
	Grabauskas et al. Lithuanian health behaviour monitoring, 2002	2002	1650	1027	20-64
	Grabauskas et al. Health Behaviour among Lithuanian adult population, 2004	2004	757	1009	20-64
	Unpublished data obtained from Sigita Mačiuikienė	*2005*	*3801*	*5707*	*15-100*
	Grabauskas et al. Health Behaviour among Lithuanian Adult Population, 2006	2006	704	1001	20-64
	Grabauskas et al, Health Behaviour among Lithuanian Adult Population, 2008	2008	715	994	20-64
	Grabauskas et al, Health Behaviour among Lithuanian Adult Population, 2010	2010	578	1359	20-64
	V. Kriaucioniene et al., The prevalence and trends of overweight and obesity among Lithuanian adults, 1994–2012, 2012	2012	716	1064	20-64
Luxembourg	Tchicaya and Lorentz, Vivre au Luxembourg, 2010	1995	-	-	16-64
	Tchicaya and Lorentz, Vivre au Luxembourg, 2010	2005	-	-	16-64
	Tchicaya and Lorentz, Vivre au Luxembourg, 2010	2008	-	-	16-64
Malta	WHO; Asciak et al, The first national health interview survey, 2003	2002	1844	2022	16-100
	National Health Survey 2007, personal communication	*2007*	*151898*	*161082*	*18-65*
	Eurostat database: European Health Interview Survey 2008 Malta	2008	-	-	18-100
Netherlands	Netherlands Central Bureau voor de Statistiek	2000	-	-	16-100
	Netherlands Central Bureau voor de Statistiek	2001	-	-	16-100
	Netherlands Central Bureau voor de Statistiek	2002	-	-	16-100
	Netherlands Central Bureau voor de Statistiek	2003	-	-	16-100
	Netherlands Central Bureau voor de Statistiek	2004	-	-	16-100
	Netherlands Central Bureau voor de Statistiek	2005	-	-	16-100
	Netherlands Central Bureau voor de Statistiek	2006	-	-	16-100
	Netherlands Central Bureau voor de Statistiek	2007	-	-	16-100
	Netherlands Central Bureau voor de Statistiek	2008	-	-	16-100
	Netherlands Central Bureau voor de Statistiek	2009	-	-	16-100
	Netherlands Central Bureau voor de Statistiek	2010	-	-	16-100
	Netherlands Central Bureau voor de Statistiek	2011	-	-	16-100
	Netherlands Central Bureau voor de Statistiek	2012	-	-	16 - ≥75
	Netherlands Central Bureau voor de Statistiek	2013	-	-	17 - ≥75
Norway	WHO: Johansson et al, 1998	1994	1461	1559	16-100
	Health Interview Survey	1998	3456	3669	16-100
	Health Interview Survey	2002	3410	3417	16-100
	WHO: Hougen HC, 2006	2005	3401	3365	16-100
	WHO: Wilhelmsen , 2009	2008	3172	3293	16-100
	Norwegian Institute of Public Health, 2012	2012	2174	2063	18-64
Poland	Eurostat database: National Health Interview Survey for Poland	1996	3137	9411	15-100
	Szponar et al. Household food consumption and anthropometric survey, 2003**	2001	1949	-	19-100
	Statistical Office Poland, personal communication	*2004*	*19335*	*19446*	*15-70*
	Statistical Office Poland, personal communication	*2009*	*11932*	*14673*	*15-70*
Portugal	Marques-Vidal et al, Ten-year trends in overweight and obesity 1995-2005; 2011	1996	38504		18-75
	Marques-Vidal et al, Ten-year trends in overweight and	1999	38688		18-75

	obesity 1995-2005; 2011				
	WHO; Carmo et al, Overweigh and obesity in Portugal, 2008**	2004	8116		18-64
	Marques-Vidal et al, Ten-year trends in overweight and obesity 1995-2005; 2011	2006	25348		18-75
	Luís B. Sardinha et al., Prevalence of Overweight, Obesity, and Abdominal Obesity in a Representative Sample of Portuguese Adults, 2012	2009	3961	5484	1 8- >75
Romania	Eurostat database: National Health Interview Survey 2002 Romania	2000	21200		15-100
	Eurostat database: European Health Interview Survey 2008 Romania	2008	18172		18-100
	Corina Aurelia Zugravu - Research Gate, Not published research	2014	711	737	18->65
Russia	Russia Longitudinal Monitoring Survey, University of North Carolina, 2011	2000	3497	4719	20-80+
	Russia Longitudinal Monitoring Survey, University of North Carolina, 2011	2001	3859	5328	20-80+
	Russia Longitudinal Monitoring Survey, University of North Carolina, 2011	2002	4034	5484	20-80+
	Russia Longitudinal Monitoring Survey, University of North Carolina, 2011	2003	4089	5570	20-80+
	Russia Longitudinal Monitoring Survey, University of North Carolina, 2011	2004	4113	5593	20-80+
	Russia Longitudinal Monitoring Survey, University of North Carolina, 2011	2005	3997	5436	20-80+
	Russia Longitudinal Monitoring Survey, University of North Carolina, 2011	2006	4969	6609	20-80+
	Russia Longitudinal Monitoring Survey, University of North Carolina, 2011	2007	4950	6587	20-80+
	Russia Longitudinal Monitoring Survey, University of North Carolina, 2011	2008	4693	6402	20-80+
	Russia Longitudinal Monitoring Survey, University of North Carolina, 2011	2009	4708	6427	20-80+
	Russia Longitudinal Monitoring Survey, University of North Carolina, 2012	2010	1140	1658	20-80+
	Russia Longitudinal Monitoring Survey, University of North Carolina, 2013	2011	7554	1545	20-80+
	Russia Longitudinal Monitoring Survey, University of North Carolina, 2014	2012	14936	20500	20-80+
	Russia Longitudinal Monitoring Survey, University of North Carolina, 2015	2013	14225	19501	20-80+
Serbia	Grujic et al, 2002*	2000	4458	4974	20-100
	Relationship between adult stature, BMI and WHR in Backa and Banat, Pavlica et al, 2009.*	2002-2006	1965	2539	20-100
	Body Height and Weight in Adult population in Srem, Banat. Tatjana Pavlica, Verica Božić-Krstić, Rada Rakić Faculty for Sciences, Department for Biology and Ecology*	2004	919	870	20 > 40
Slovakia	Eurostat database: National Health Interview Survey 2002 Slovakia	2002	1569	-	15-64
	Annual Health Report, Slovak Public Health Authority, personal communication	*2006*	*1393*	*1443*	*15-65*
	Eurostat database: European Health Interview Survey 2008 Slovakia	2009	1457	1423	15-65
	Annual Health Report , Slovak Public Health Authority, personal communication	*2010*	*1437*	*1438*	*15-65*
Slovenia	Eurostat database: National Health Interview Survey 2002 Slovenia	2001	1097		15-100

	Eurostat database: European Health Interview Survey 2008 Slovenia	2007	2118		18-100
Spain	National Statistics Institute online database, National Health Survey 2003	2003	16296	17248	18-100
	National Statistics Institute online database, National Health Survey 2006	2006	16911	16478	18-100
	National Statistics Institute online database, National Health Survey 2009	2009	17558	17718	18-100
Sweden	WHO; Swedish Survey of Living Conditions	1999	5587	5762	16-84
	WHO; Swedish Survey of Living Conditions	2001	5515	5838	16-84
	Statistics Sweden, personal communication	*2004*	*2742*	*2849*	*16-84*
	Statistics Sweden, personal communication	*2008*	*11118*	*-*	*16-84*
	WHO; Enkätundersöknin 2009, Det nationella urvalet	2009	4570	5604	16-84
	Statistics Sweden, personal communication	*2011*	*2633*	*2914*	*16-100*
	Statistics Sweden, personal communication	*2012-2013*	*9931*	*9765*	*16 - >85*
Switzerland	WHO: Enquete Suisse sur la Sante 2003	1992	6749	8150	15-100
	WHO: Enquete Suisse sur la Sante 2003	1997	6716	7105	15-100
	WHO: Enquete Suisse sur la Sante 2003	2002	8843	10629	15-100
	WHO: Enquete Suisse sur la Sante 2009	2007	8339	10134	15-100
	Swiss Statistics	2012	3 350 658	3487610	15 - >75
England (as a proxy for United Kingdom)	Health Survey for England*	2003	6519	6570	16-100
	Health Survey for England*	2004	2772	2812	16-100
	Health Survey for England*	2005	3144	3184	16-100
	Health Survey for England*	2006	6014	6074	16-100
	Health Survey for England*	2007	3008	2983	16-100
	Health Survey for England*	2008	6385	6450	16-100
	Health Survey for England*	2009	2055	2045	16-100
	Health Survey for England*	2010	3563	3523	16-100
	Health Survey for England	2011	3478	3530	16-100
	Health Survey for England*	2012	3475	3495	16-100
	Health Survey for England*	2013	3688	3763	16-100
	Health Survey for England*	2014	-	-	16-100
Uzbekistan	WHO: Demographic and Health Survey*	1996	-	4038	15-49
	Demographic and Health Survey*	2002	2058	4967	15-65
	Estimated from GBD mean data[2]	2008	-	-	-

1. Literature review protocol

A comprehensive review of the published and grey literature was performed, according to the following protocol: To review the prevalence of risk factors for liver disease (alcohol consumption, obesity, viral hepatitis and health inequalities) and their strength of association with different liver disease types and mortality.

Peer reviewed literature sources included PubMed: reviews and meta-analyses articles. For grey literature sources Google, national public health websites were searched.

Sources included reviews, meta-analyses, comparative studies and evaluation studies and surveillance studies. Inclusion criteria included an up to date effect estimate for relationship between determinants/ risk factors and liver disease, for any of the 35 HEPAHEALTH countries prevalence of the determinant/risk factor, by age/sex group and for as many years

as possible. Determinants of interest were extracted age and sex and socio-economic status (where possible), in the general or clinical populations, with no age restrictions. Alcohol consumption, prevalence of obesity by WHO cut-offs, incidence and prevalence of viral hepatitis (B and C) infection (to supplement any data from *Part 1. The current and historical burden of liver disease in Europe*) were collected.

Data eligible for inclusion should be presented in Relative risk ratio (RR), Odds ratio (OR), Hazard ratio (HR) with associated confidence interval/uncertainty estimates for effect estimates and Prevalence (rate per 100,000) or percentage population with relevant denominator information. No language restrictions were applied (translation of non-English publications will be performed where possible; any exclusions will be documented). Data since 2005 or overlapping with 2005 were extracted for risk factor prevalence and effect-estimates for non-mortality related liver disease. Studies with liver mortality as outcome are allowable from 1995.Data presented disaggregated by sex, age, and other socioeconomic data if available, in particular for the latest available data point (as this will be used in the later modelling project).

Literature was excluded if they provided data on conditions with generally short-term/acute with good recovery rates, or are relatively rare compared to the included conditions, such as pregnancy-related liver disease as acute, gallstones, drug-induced acute liver damage, and if they focussed on non-modifiable risk factors including genetic and autoimmune factors.

Included literature was graded according to the NICE checklist review will be used to rate the quality of data from reviews

Data extraction was performed using a form in MS Excel, using the following header list:

Table 15. Data extraction header list

Reference id	Determinant category (i.e. BMI; alcohol; viral hep, other)	Statistical analysis method
URL	Result type (Effect/association estimate; prevalence data)	Metric/unit
Author	Year data collected	Key results
Year of publication	Study type (cohort, cross-sectional)	
Region	Sample size	
Country	Age group	
Urban/Rural	Sex	
Population represented (national; subnational, other)	Ethnicity/ SES	

2. Additional data on diabetes not standardised but aggregated across all ages 20-79, with data prior to 2007.

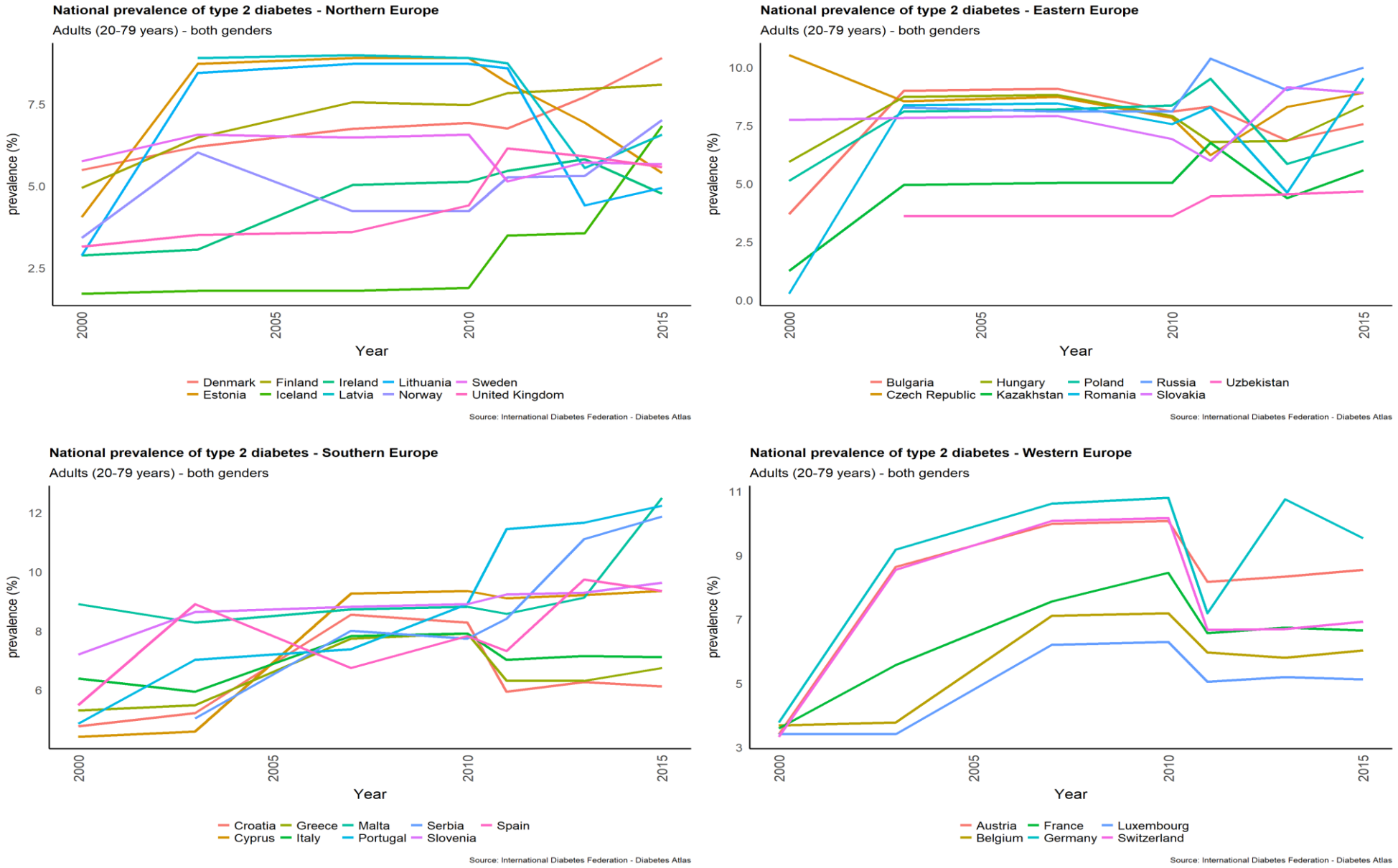


Figure 82. Prevalence of type 2 diabetes for male and female adults (20-79 years) by UN subregion

Qualitative expert interview

Rationale

Expert testimony and qualitative analysis is useful for enriching our understanding of how and why liver disease mortality has changed over time and the limitations of measurements and data across Europe. This qualitative study supplements part one and two of the HEPAHEALTH project.

This study used thematic framework analyses to extract underlying themes from in-depth interviews on the determinants of liver disease and changes in morbidity and mortality over time.

Methods

Participant information and recruitment

Interviews were carried out with medical professionals, patient organisations, public health specialists, epidemiologists, public health and clinical data analysts and EASL contacts.

Known experts were identified and invited to take part in qualitative interviews via email. Interviews were carried out until thematic saturation was reached. In total, seven experts from a range of European countries/disciplines were interviewed. All interviews were conducted in English and interviewees were anonymised with an ID from 1 to 7. Participant information was held on a password protected computer.

Participants were asked to read a participant information sheet and complete a consent form ahead of the interview. They were informed that they could withdraw from the study at any time. All people who expressed an interest in being interviewed consented to take part. All interviews were recorded and transcribed verbatim.

In order to supplement these interviews, two focus groups with seven additional liver disease experts were conducted. The questions from the interview topic guide were split between the two groups of three and four respondents. While the focus groups were not recorded or transcribed verbatim, their responses and themes were incorporated by the researchers familiar with both the in-depth interviews and the focus groups.

Topic guide

Following the literature reviews and discussions with the steering team a standard topic guide was developed and is summarised in Table 16. From this, a semi-structured interview was conducted. Priority was given to asking the most open and neutral questions possible. Participants were given some background to the HEPAHEALTH project, and told that the purpose of the interview was to gain a deeper understanding of the determinants of liver disease mortality across their country/region and Europe. The guide was used flexibly and prompts were used as necessary. One pilot interview was carried out to approximate interview length and ensure that the topic guide was understood.

Table 16: Interview topic guide used for the semi-structured interviews

1. Can you tell me about your work in liver disease? (Prompts: how long have you been working in liver disease? What roles? Which contexts/countries/regions?)
2. Can you talk a little bit about how liver disease has changed in your country/region over time?
3. How general is this to your region? (prompt: how does it compare to neighbouring countries)
4. What do you think are the main barriers to good liver health/risk factors for liver health in your country?
5. What factors could improve liver health/liver disease outcomes in your country?
6. What would you prioritise in terms of liver disease prevention and treatment in your country? Why?
7. Are any population groups in your country affected more than others by different types of liver disease? Why do you think this is?
8. How do you see the future of liver disease in your country?
9. Can you talk a little about liver disease surveillance data in your country?

Prompts if further details required:

a. Describe other metrics not mentioned e.g. incidence, prevalence, costs, survival
b. What are the gaps in data?
c. What are strengths/weaknesses of the data?
d. Can you describe the data quality in your region/country?
e. Request that they complete the online survey, to be emailed to them

Analysis

All interview data were checked for accuracy by re-listening to the recording while reading the transcript. Thematic framework analysis was undertaken to categorise experts' perceptions into themes and sub-themes.[222] Refinement of codes and themes occurred throughout the analytic process. Thematic analysis is a useful way of managing, ordering and filtering large amounts of interview data. The thematic analysis stages set out by Pope *et al.* (2000) were followed.[223]

1. Familiarisation with transcripts.
2. Identification of a thematic framework: Using Nvivo software, an initial set of nodes was created to reflect the themes and subthemes set out in the topic guide.
3. Assignment of text to the most appropriate node or nodes ('indexing'). This included the addition of further nodes to the framework to include emerging themes/sub themes. Text was coded more than once if it conveyed more than one meaning, and coded extracts included in as many different themes as was relevant. Two researchers independently coded each transcript. To check the validity of the themes, and coding consistency, the percentage agreement and disagreement between the two researchers was calculated. Coding disagreements >15% (or >10% if the second researcher had coded 0% for a particular node) were discussed and resolved. This helped ensure consensus in our interpretation of the data.
4. Summarising opinions and experiences under each theme or sub-theme ('charting').
5. Assessment of the consistency of responses and identification of discrepant responses (and possible reasons for discrepancies). Links between themes were

assessed to reveal patterns within the data and to guide the interpretation of narrative accounts (‘mapping and interpretation’).

Results

Figure 83. The hundred most common words from all HEPAHEALTH qualitative interviews

The 100 most common words from the HEPAHEALTH interviews are shown in Figure 83 and illustrate that most interviewees focused on the morbidity and mortality of viral hepatitis and alcoholic liver disease. One thing to note is that the word change is quite prominent, and throughout the interviews experts were calling for a change in the way that liver disease is diagnosed, treated and considered by the healthcare system and the way liver disease is communicated to the public. It was suggested that this type of change was the future of reducing the burden of liver disease. Figure 83 also illustrates that hepatitis still dominates the conversation around liver disease. However as the quantitative data demonstrates, in Europe, the morbidity and mortality burden from alcoholic liver disease is much greater than for viral hepatitis. Qualitatively this was explained by the fact that hepatologists are not trained to deal with alcohol as a social disease and by expanding and working with other health care professionals alcoholic liver disease may become better understood in the healthcare system.

Seven individual in-depth semi-structured interviews were recorded, transcribed and used in the following analysis. The participants came from a range of European countries, including one each from Croatia, Italy, Poland, Portugal, Russia and two from the United Kingdom.

The respondents came from a variety of professional backgrounds, including academic and clinical fields of gastroenterology, hepatology, transplantation and infectious disease and patient associations. Several (n=4) had a mixed experience of both academic and clinical experience in the field of liver disease. Some interviewees had experience across liver disease specialities, while others had focussed work in one area. Specialities were generally infectious disease and viral hepatitis but participants also specialised in transplantation and non-alcoholic fatty liver disease/ non-alcoholic steatohepatitis (NAFLD/NASH). The seven liver disease experts interviewed in two focus groups represented Poland, Serbia, Portugal, the United Kingdom, Switzerland, Bulgaria and Belgium.

The results of this study are presented here by integrating the responses to the interviews and the focus groups around four main topics, trends in liver disease, barriers to good liver health, future priorities, and expert recommendations.

Geographic trends in liver disease over time.

Participants discussed trends in liver disease in their countries and the European region along different dimensions, as described below:

<u>The current burden of liver disease within participants' country/region</u>

While most participants discussed a decrease in the rate of viral hepatitis and an increase in alcohol and obesity-driven liver disease, participants did recognise different patterns in their countries and regions.

Viral hepatitis was by far the most commonly discussed liver disease, mentioned by all participants, followed by alcoholic liver disease and obesity-related/NAFLD mentioned by six and five participants respectively. Less frequently discussed diseases included autoimmune and metabolic diseases, which were only mentioned by four out of seven interviewees. Participants were not always in agreement as to the most prevalent cause of liver disease within the same region for example, the two participants from the United Kingdom had differing statements as to why liver disease was increasing in the population, one suggesting it was increases in alcoholic liver disease and the other arguing the increasing trend was due to obesity.

When discussing within country trends in liver disease, several respondents were keen to point out regional differences in the types of liver disease.

There are some differences between North and South [country]. It's a small country, but there are some differences. We have, for example, more hepatitis B and more hepatitis C in the South. Um, alcohol very rightly, slightly higher in the North. And the autoimmune diseases are spread all over the country but the prevalence of autoimmune is not very high. (ID:1)

<u>Changes and causes of change of liver diseases within countries</u>

A geographic pattern emerged showing that moving from Western to Eastern Europe the importance of NAFLD/NASH and alcoholic liver disease decreased, while hepatitis infection increased. Respondents often referred to a 'shift', whereby in Western European countries

as rates of hepatitis B and C have decreased they can now clearly see a shift towards non-communicable causes of liver diseases, such as alcohol and obesity. Respondents from Eastern countries are still heavily focussed on viral hepatitis as the main liver disease of concern.

Subgroups affected by liver disease

While trends were examined for the whole country in general, several participants of both interviews and focus groups also discussed population subgroups in more depth. Answers revealed the liver disease map to be extremely fractured, with different population groups at risk and exposed at different periods of life.

Several respondents agreed that fatty liver disease was the most homogenous liver disease saying the obesity problem is transverse to the population:

So no specific groups or professions or…it's, the non-alcoholic fatty liver disease is epidemic, so everyone will have. (ID:1). Several experts noted the emerging risk of childhood obesity and metabolic syndrome as an important future driver of the burden of liver disease.

For other aetiologies of liver disease, different populations were often mentioned to be more affected than others. When discussing alcohol, it was noted that there is an emerging increase in consumption for women compared to men, leading to a shift in the burden of alcoholic liver disease in women. Respondents also noted that the majority of alcoholic liver disease is focussed in extremely high alcohol consumers and this behaviour can be limited through local policies and actions within countries.

Alcoholic liver disease and viral hepatitis are very highly clustered. Not only in areas of deprivation because there's a very strong linkage with health inequalities, but also probably as a result of micro-cultures within those drinking environments. (ID:2).

Several participants mentioned the particularly high risk of cirrhosis and hepatocellular carcinoma in the baby-boomer generation and risk of viral hepatitis coming from migration from high burden countries. Saying

we also need to be looking at specific populations which are most likely to be affected with viral hepatitis and the classic groups there are if you like the baby boomer generations, and people who … may have used illicit drugs in the past and so on but they're not exclusive groups – it's much broader than that of course (ID:4).

This must be contrasted with respondents from Eastern Europe who highlighted the increased burden of hepatitis B and C infection in a younger cohort.

The future of liver disease

The majority of respondents expected hepatitis B and C to reduce dramatically in future years, this view was particularly prevalent in countries where infection control measures, including universal immunisation and access to hepatitis C therapy was available.

I believe that the impact of chronic hep B and C is very high for this negative trend, and I think if the situation will not change with better access to antiviral treatment we will definitely

see higher proportion of patients with negative outcomes and definitely the mortality due to liver cirrhosis and liver cancer [hepatocellular carcinoma] will increase. (ID:7)

Alcohol was seen as a problem that was not going away. Obesity was mentioned to a lesser extent as a risk factor which was likely to lead to further increases in liver disease morbidity and mortality.

Uncertainty in the data on liver disease

Participants frequently mentioned uncertainty in the data on which they were basing their opinions. They attributed this uncertainty to several factors, ultimately suggesting that

the degree of uncertainty comes about as a result of clinical coding. So liver mortality and admissions are coded using ICD-10 codes, and historically those ICD-10 codes aren't really applicable to modern liver disease. You know, some of the terms are completely meaningless (ID:2).

They also noted a lack of studies on the burden of diseases, particularly hepatitis B.

The main barriers or risk factors to good liver health in European countries

Participants were very aware of a large number of barriers to liver health across Europe. Table 17 summarises these barriers through participant quotations. The problems currently identified by respondents can broadly be categorised into four levels of determinants: such as individual behaviours, societal and healthcare barriers, and finally barriers at the distal level, including the political and economic context.

Table 17. Identified barriers to good liver health

Behavioural barriers
Alcohol
We know that alcohol related harm is a dose-dependent phenomenon at an individual level. The more you drink, the more all of the different types of alcohol related harm increase, and the same holds at a population level. The more a country drinks, the higher the level of alcohol related harm. (ID:1)
Obesity
We have 25% of obesity in terms of population. So we expect around half of these patients, half of this people have some sort of liver disease. So we expect at least more than one million people have NASH [Non-alcoholic Steatohepatitis], I wouldn't say NASH, at least NAFLD, at least some fatty liver disease. More than one million for sure. (ID:2)
Diabetes & the metabolic syndrome
If you have diabetes plus obesity these conditions do increase the risk of hepatocellular carcinoma which is something very new we are not used to seeing. (ID:3)

Struct

I think there is a population of Injecting Drug Users which increase the risk of transmission of hepatitis C [which] exist[s] still in the community were they have the exchange of drugs and adding to that there's unfortunately a number of people at risk of taking the new drug. (ID:3)

Other

Maybe you had a tattoo, maybe you shared a toothbrush with somebody who experimented with drugs or had a tattoo you know the list of ways you can come to liver disease is broad and diverse. (ID:4)

Social barriers

Late-presentation with liver disease

75% of people with cirrhosis in [my country] right now, don't know they have a liver problem, and the first they'll know about it is when they're admitted with bleeding oesophageal varices or their liver ascites, fluid in their tummy, or with liver cancer, or with jaundice .(ID:2)

Low awareness of liver disease

We need to have a recognition that people need to be aware of the importance of their liver health, and that's really a generic statement, so it doesn't matter what liver disease you're talking about - greater public awareness about liver problems is important. (ID:4)

Health system barriers

Diagnostics and screening in health system:

We need to be accurately diagnosing patients … so we need effective non-invasive testing to identify the right patients – particularly to risk stratified patients – the ones who are most likely to develop progressive liver disease and experience associated morbidity and mortality. (ID:4)

Health care capacity and training:

we also have relatively low rates of physicians and nurses, per 100,000 inhabitants. And it's a major barrier, because for example in my department, to get to hepatological outpatients, some patients which do not have urgent indications, need to wait many months, not weeks, but months, on the waiting list. (ID:5)

Structural/system barriers

Government and policy

What is lacking of is political decisions. I mean in terms of so called national plans for this and for that. We don't have a national plan for liver diseases. (ID:1)

Financing:

The problem is always money – it is a financial problem, especially if we are talking about rare diseases. (ID:6)

Industry

We have a very very powerful drinks industry. They're very well organised. They've learnt an awful lot from tobacco regulation, about how to obstruct regulation. About how to

infiltrate themselves within government, and indeed with the department of health. The department of health spends a lot more time speaking to the drinks industry than it does with the hepatology profession for example. That's the department of health, not trade and industry. (ID:2)

The future priorities of liver disease in European countries

To understand future priorities for liver disease each respondent was asked what their priorities were for the future. Their responses focused on education, both of medical professionals and the public, health system changes and social factors.

Diversifying liver disease expertise

Interviewed experts recommended that awareness of liver disease in both the medical and public spheres be increased. Improving knowledge and awareness of liver disease amongst GPs can lead to earlier diagnosis, and therefore could help prevent rising levels of liver disease. At the moment most liver disease cases are identified in hospital and by improving GP education the health system can focus more on prevention and management of liver disease.

One suggestion for reducing late diagnosis of liver disease was to provide specific training for GPs, by

bringing up the general practitioners into the scientific arena in terms of liver diseases which is not easy. And it is controversial. … It's not bringing the people into the hospital, it's getting there, getting near to the people, and the best way is of course with the general practitioners.(ID:1)

The skills needed to detect liver disease can be built into the daily work of a GP. In order to standardise and regulate liver disease care amongst GPs it was suggested that tests for liver disease be added as part of the medical practitioners annual incentive/reward programme, the Quality Outcomes Framework (QOF).

One of the obvious things to do is within primary care, the primary care physicians, the general practitioners, they're salaried the funds their practice receives are governed by certain quality indicators, such as QOF points – at the moment there is no points for assessing liver disease – checking people's liver function tests even basic biochemistry and so a really important step here is for there to be points associated with assessing liver disease risk and I think that would be the single most important thing that we could achieve because then it would mean that primary care physicians have an even stronger motivator to seek out patients across all forms of liver disease. (ID:4)

By encouraging GPs to have these conversations with their patients this ensures that risk factors related to liver disease are more readily discussed at regular patient and physician interactions in the health care system.

Improving public awareness

Liver disease provides its own example of how increasing awareness can help decrease prevalence. Various public health promotion campaigns have helped to reduce the burden of

viral hepatitis. While there is still work to be done in combating viral hepatitis, they provide an example of effective liver disease prevention strategies, which are easily actionable.

In the year 2010 the World Hepatitis was officially adopted not adopted but announced by WHO and the things and the picture and the situation at the European level has significantly changed of course in a positive way because the recognition of hepatitis as a public health problem has arised also at the governmental level not only among experts and doctors and patients but also at the governmental level. (ID:6)

Raising awareness has been shown to affect health outcomes, and most experts wanted to work with the media and government to educate the public around the risk factors, causes and treatments of liver diseases. Often respondents focused on Hepatitis C as a 'quick win' which could pave the way for policies and treatments targeting other liver diseases.

My strategy would be first of all, bringing the liver diseases into the media. The best way is getting something that we can easily and rapidly control. I mean in terms of diagnosing and treating. And for sure that is hepatitis c… And if we make lots of noise, we are doing that. We are trying to do that, about hep C. After that, we can manage to bring some of the other diseases. …. So we have to take a good example, … look at this one. It's straight. We can deal with it. Then people will become aware that there are abnormal liver function tests, there are things that we can look for, there are things that we can very easily understand. (ID:1)

Given that liver disease is often believed to be confined to at risk groups, public education needs to focus on the diversity of liver disease and its prevalence within communities. By addressing the social barriers identified in Table 17 and providing targeted education regarding these barriers to the population and to those that are most at risk.

<u>Treatment and policy actions</u>

In order to curb the rise in liver disease morbidity and mortality it is recommended that the public, academic and political community are made aware of how burdensome liver disease is, both to population health and the economy. There is a need for governments to invest in liver disease prevention programs, such as alcohol taxes, vaccines and health lifestyle programs, all of which have been shown to reduce liver disease mortality and morbidity by reducing the incidence of advanced liver disease. The medical community can work in parallel to improve treatment and prevention at the person level and to be strong advocates for reducing the burden of liver disease.

Ensuring that everyone has affordable access to treatment and vaccines will reduce the morbidity and mortality of liver disease. Past policies have shown that mortality for some liver disease can be reduced by behavioural changes and, importantly, these affects can be seen rather quickly. The challenge is to convince governments of the benefits of the actions and why they are beneficial in both the long and short term. Alcoholic liver disease has that advantage as

people come into hospital as a result of acute or chronic liver failure as a result of their recent drinking, and as soon as they stop drinking that starts to appear on the survival curve almost immediately, and the converse happens. … There aren't many public health policies where a change in government policy has an almost immediate readout in terms of alcohol

morbidity and mortality. …so alcohol policy is an example of somewhere where that does happen. (ID:2)

As the above quote illustrates interventions that impact heavy drinkers have been shown to have quick and positive effects on liver mortality. Implementing alcohol policies, such as taxes and a duty escalator shows evidence of having positive affects for reducing liver disease mortality. These changes also have economic benefits that make them attractive to governments.

All respondents were quite optimistic about possible new drugs to help treat liver diseases such as viral hepatitis. Equally there was a common belief that vaccines for hepatitis C would be soon available and that universal vaccination is a future priority.

I believe that we will observe, … maybe in 30 years hepatitis C will really disappear with a new drug. I believe hepatitis B will stay despite we have a very good drug to treat, will be quite stable for at least another 20 years. (ID:3)

Respondents were quick to note that despite the successes of treating viral hepatitis, the rising burden of NAFLD/NASH must be addressed due to the changing characteristics of people affected by liver disease.

Before treating patients, the health system must accurately diagnosis patients. While the respondents recommend shifting liver disease conversations to GPs for earlier diagnosis, there is a continued need for new diagnosis tests and for support treatment.

The next thing is to provide the tools for primary care so that they can best assess risk stratified people so that's guidelines in terms of fatty liver disease in terms of the people most likely to have problems and also cost-effective ways of identifying the people most likely to have those issues at present. (ID:4)

The healthcare system will need to adapt to ensure effective diagnosis and support for patients who must adjust their lifestyle to improve their health.

All respondents were weary of the resource and governmental challenge of ensuring maximum vaccine coverage and support for patients at all levels in the health system. This was acknowledged as a challenge for governments and the healthcare system, but one that would ultimately improve health and reduce economic burden of liver disease. Already there are many governments and other organisations working together within Europe and wider afield to help reduce liver disease mortality and morbidity.

Expert recommendations and thoughts

The liver doesn't have any pain receptors, there are little to no symptoms of liver disease and reliable tests for various types of liver disease do not exist. Given this, throughout the qualitative interviews specialists discussed that a key way to reduce liver disease burden is through a paradigm shift in the way that liver disease is dealt with in the healthcare system. This includes reducing the stigma of liver disease, educating GPs, early diagnosis, and enacting targeted policy.

By shifting the conversation of who is affected by liver disease, specialists hope that policies and diagnosis activities will follow suit. As previously discussed policies for alcohol

management have been shown to effectively decrease the mortality and morbidity of alcoholic liver disease. Interviewees were thinking of ways to better talk about alcohol in the public sphere to try and de-normalise excessive drinking. However, there are cultural, societal and political forces that make this conversation more difficult. If a paradigm shift occurs then perhaps these barriers can be successfully navigated, through earlier diagnosis and targeted policy and government support. Ultimately the aim of the intended paradigm shift is to help liver disease experts get to the right people at the right time.

Liver disease has historically been talked about as predominately affecting specific at-risk populations, including people who use injection drugs and people who consume excessive amounts of alcohol. However, interviewees spoke about the need to reframe the population affected as liver disease is more common than the public, and to some extent GPs, understand. There are many lifestyle behaviours that can increase the risk of someone developing liver disease and

people need to understand that liver disease isn't just affecting stereotypical people for example who drink too much – it's a condition that can affect you if you're overweight, if you have a metabolic syndrome, it can affect you if maybe you experimented with drugs many years ago – maybe you had a tattoo, maybe you shared a toothbrush with somebody who experimented with drugs or had a tattoo you know the list of ways you can come to liver disease is broad and diverse so it's very important that people understand that those risks are present (ID:4).

Patient groups warn that liver disease transmission goes unreported due to stigma, further reducing the effectiveness of the healthcare system.

Improvements in detecting and diagnosing liver disease is a fundamental priority for the future and a common cause for concern amongst those interviewed. At the moment there is concern that the tests used for detection of liver disease are only capable of picking up certain types, specifically through enzymes that have escaped the liver. However alcohol and obesity related liver disease cannot be detected in the same way as in these diseases the liver membrane remains intact. Thus the health system

is built around detecting necro-inflammatory processes, whereas 90% of liver mortality is from a different type of process which those tests don't detect (ID:2).

Discussions about how to reframe the medical detection of liver disease are beginning to happen in some regions but ultimately the need to shift the conversation around liver disease must be dealt with in order to have meaningful reductions on mortality and morbidity.

Interpretation

As the focus groups discussed,

the fact that the vast majority of liver mortality is ultimately preventable, and preventable by a few simple, very cheap income generating things. So there's a lot to play for (Focus group).
The qualitative interviews provide a real time picture of the burden of liver disease across Europe. This work has simultaneously highlighted key priorities for the liver disease experts to pursue in the future and the key barriers they face. By achieving earlier diagnosis, through more advanced tests and taking advantage of patient contact with GPs, the burden of liver disease can be reduced. By working together, governments and health professionals can

de-stigmatise liver disease by illustrating the many types liver diseases, they can work to reduce risky lifestyle behaviours through targeted policy and public health education. Liver experts have demonstrated that these actions help to reduce the burden of liver disease and are required to stop the continued rise in liver disease morbidity and mortality.

Strength and limitations

This study used a flexible mixed-methods approach to understand the complexities of liver disease in Europe. While the sample was self-selected and small, there was a common saturation of themes. Thus the number of interviews was deemed adequate for the timeline of the study. The interviewees came from a variety of disciplines, countries and fields of expertise ensuring that the sample is not biased towards one type of liver disease or geographical location. There is a future opportunity to further analyse the online survey emailed to the entire HEPAHEALTH network.

Conclusion

While the qualitative interviews indicate that liver disease varies across countries, one thing that most interviewees agreed with was that

> *we really are in a poor position. But the only advantage of that is that things sort of can only get better really. They're going to get worse first unfortunately (ID:2).*

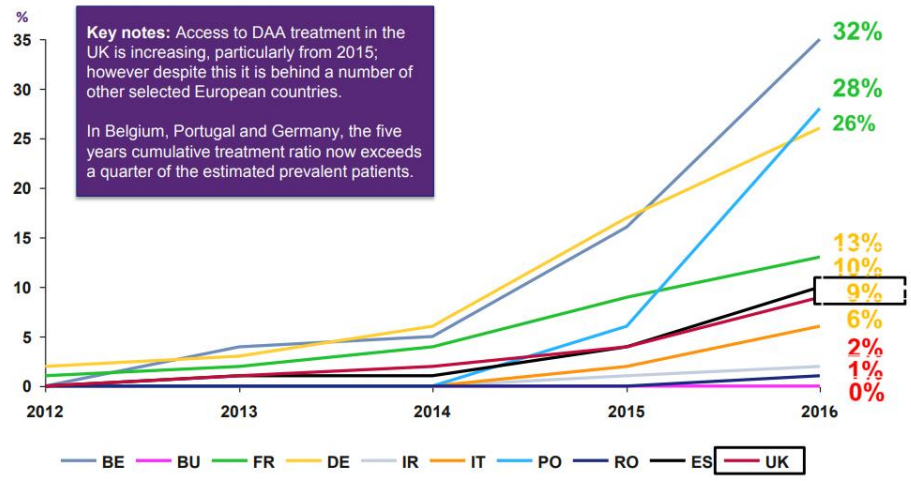
The future of liver disease can be altered quickly and economically through simple improvements in diagnosis and education, and through the enactment of economically advantageous policy. To reduce the burden of liver disease it is key that late stage diagnosis is reduced. Experts believe this can be done through regular conversations about liver disease and its risk factors within the health system, by improving physician knowledge of liver disease and how to diagnosis it and simultaneously improving diagnostic tools liver disease. Implementing policy such as duty escalators or taxes can reduce the burden of alcoholic liver disease and other types and save lives. Future liver disease priorities are about advocating for a paradigm shift to change the way that liver disease is addressed in the healthcare system. This shift would help experts work with governments to ensure effective policy and tools can be implemented to reduce the burden of liver disease in specific populations but also the wider population.

Supplementary material for Part 3

Table 18. Year of first introduction of hepatitis B containing vaccine in the entire country reported annually through the WHO/UNICEF joint reporting process[224]

Country	GAVI eligible country (2016)	Vaccine in schedule (as of 31 December 2016)	Year of introduction in entire country	Year of introduction in part of the country	HepB Birth Dose in schedule (in 2016)	Birth Dose offered to all children	Year of introduction of Birth dose
Austria	No	Yes	1997	n/a	No	n/a	n/a
Belgium	No	Yes	1996	n/a	Yes(R)	n/a	n/a
Bulgaria	No	Yes	1991	n/a	Yes	yes	prior or= to 1998
Croatia	No	Yes	1999	n/a	No	n/a	Was vaccinating from 2007-2014.
Cyprus	No	Yes	1989	n/a	No	n/a	n/a
Czech Republic	No	Yes	2001	n/a	Yes(R)	n/a	n/a
Denmark	No	Yes(R)	n/a	n/a	Yes(R)	n/a	n/a
Estonia	No	Yes	2003	1999	Yes	yes	2003
Finland	No	Yes(R)	n/a	n/a	n/a	n/a	n/a
France	No	Yes	1994	n/a	Yes(R)	n/a	n/a
Germany	No	Yes	1995	n/a	No	n/a	n/a
Greece	No	Yes	2000	n/a	Yes(R)	n/a	n/a
Hungary	No	Yes(A)	n/a	n/a	n/a	n/a	n/a
Iceland	No	Yes(R)	n/a	n/a	n/a	n/a	n/a
Ireland	No	Yes	2008	n/a	No	n/a	n/a
Italy	No	Yes	1982	n/a	Yes(R)	n/a	n/a
Kazakhstan	No	Yes	1998	n/a	Yes	yes	1998
Latvia	No	Yes	1997	n/a	Yes(R)	n/a	n/a
Lithuania	No	Yes	1998	n/a	Yes	yes	1998
Luxembourg	No	Yes	2000-2003	n/a	Yes(R)	n/a	n/a
Malta	No	Yes	2005	n/a	No	n/a	n/a
Netherlands	No	Yes	2011	n/a	Yes(R)	n/a	n/a
Norway	No	Yes(R)	2017	n/a	Yes(R)	n/a	n/a
Poland	No	Yes	1997	1995	Yes	yes	prior or= to 2001
Portugal	No	Yes	1994	n/a	Yes	yes	2000
Romania	No	Yes	1995	n/a	Yes	yes	prior or= to 1998
Russia	No	Yes	2000	n/a	Yes	yes	2000
Serbia	No	Yes	2006	2002	Yes	yes	2006
Slovakia	No	Yes	1998	n/a	Yes(R)	n/a	n/a
Slovenia	No	Yes(A)	n/a	n/a	Yes(R)	n/a	n/a
Spain	No	Yes	1996	1991	Yes	yes	prior or= to 2003
Sweden	No	Yes	2016	2014	Yes(R)	n/a	n/a
Switzerland	No	Yes(A)	n/a	n/a	Yes(R)	n/a	n/a
United Kingdom	No	Yes(R)	2017	n/a	Yes(R)	n/a	n/a
Uzbekistan	No	Yes	2001	1997	Yes	yes	prior or= to 1998
Yes (A) stands for adolescent							
Yes (R) stands for "Risk groups"							

The cumulative percentage of patients treated of the prevalent population in the last 5 years



[1] AbbVie Data on File, IMS Health report for ABPI VHI: Hepatitis C Treatment in Europe, AXDoF162070

Slide 4

The DAA treatment ratio versus prevalence (slide 2 of 2)

	Estimated Prevalence	Treatment Courses	Cumulative Ratio Treatments/ Prevalence
ITALY	1,555,580	91,144	6%
SPAIN	795,090	74,386	10%
ROMANIA	644,708	3,722	1%
FRANCE	429,195	52,510	13%
GERMANY	241,860	57,471	26%
UK	214,000	17,695	9%
BULGARIA	108,900	115	0%
PORTUGAL	56,484	13,425	28%
IRELAND	55,080	1,238	2%
BELGIUM	13,440	4,090	32%

Key notes: This table provides the background information reflected on the previous slide, in ascending order based on estimated prevalence.

Germany and the UK have been highlighted as two countries with similar prevalence figures. However, there are significant differences in the number of DAA treatment courses and resulting cumulative ratio of treatments vs prevalence providing an explanation as to why the UK is rated 'amber' rather than 'green'.

[1] AbbVie Data on File, IMS Health report for ABPI VHI: Hepatitis C Treatment in Europe, AXDoF162070

Slide 7

Figure 84. Slides on DAA access and uptake in selected European countries.