# EASL-Lancet Commission on Liver Disease in Europe

## Supplementary Appendix to Commission Report

**Supplementary Appendix Table of Contents**

**The EASL-Lancet Commission on Liver Disease in Europe**

The European Association for the Study of the Liver (EASL) and The Lancet commissioned this report in 2018.[1] Prior to the Covid-19 pandemic, three physical Commission meetings delineated the overall scope of the analysis and the narrative and emphasis of the reporting. Meetings April 30th-May 1st 2018 and August 28th-29th 2019 were hosted at the EASL headquarters in Geneva, Switzerland, and the meeting January 20th-21st 2019 was hosted at The Lancet editorial office in London. The Covid-19 pandemic introduced a delay in the working of the commission, and all meetings after Covid-19 have been hosted digitally, mostly at Working Group level. The composition of the EASL Lancet Commission is listed below. The Commission also engaged with research groups outside of the formal structure, and the named list of ICMJE qualified authors reflects actual contributions to the content of this report.

Roadmap: The EASL-Lancet Commission report spans seven "virtual chapters":

**Chapter 1.** *A new era of European Hepatology*

**Chapter 2.** *The burden of liver disease based on a European landscape of risk factors*

**Chapter 3.** *Inequalities and the next generation of liver disease patients*

**Chapter 4.** *Stigma and discrimination exacerbate inequalities for liver disease patients*

**Chapter 5.** *Moving from treatment of complications to case finding, screening and prevention*

**Chapter 6.** *A call for action to improve European liver health*

**Chapter 7.** *Future perspectives*

## Members of the EASL-Lancet Commission on Liver Disease in Europe

| Commissioner | Country |
|---|---|
| Belloni, Annalisa | UK |
| Bugianesi, Elisabetta | Italy |
| Burra, Patrizia (co-chair) | Italy |
| Buti, Maria | Spain |
| Carrieri, Patrizia | France |
| Cortez-Pinto, Helena | Portugal |
| Dusheiko, Geoff | UK |
| Flisiak, Robert | Poland |
| Gines, Pere | Spain |
| Hatzakis, Angelos | Greece |
| Hutchinson, Sharon | UK |
| Karlsen, Tom Hemming (co-chair) | Norway |
| Kelly, Deirdre | UK |
| Lazarus, Jeffrey V. | Denmark/Spain |
| Maevskaya, Marina | Russia |
| Manns, Michael (co-chair) | Germany |
| Martin, Natasha | US |
| Newsome, Phil (EASL Secretary General) | UK |
| Ninburg, Michael (patient representative) | UK / WHA |
| Pryke, Rachel | UK |
| Reic, Tatjana (patient representative) | Croatia / ELPA |
| Rhodes, Tim | UK |
| Sangro, Bruno | Spain |
| Sheron, Nick | UK |
| Simonova, Marieta | Bulgaria |
| Yki-Järvinen, Hannele | Finland |
| Zelber-Sagi, Shira | Israel |

## Working groups of the EASL-Lancet Commission on Liver Disease in Europe

1. Burden and (prevention) policy incl. policy makers
2. Stigma, human rights and the patients' voice
3. Primary and community care incl. testing and access to care
4. Educational framework to support standards (all target groups)
5. Fatty liver disease (both alcohol and metabolic) reference group
6. Viral liver diseases reference group

7. Rare diseases and paediatrics reference group
8. Liver oncology (incl. palliative care and transplantation) reference group
9. Decompensated liver disease (incl. palliative care) reference group

**Members of the EASL-Lancet Commission Working Groups (WGs)**

| WG 1 | Role | Country |
|---|---|---|
| Nick Sheron | Chair | UK |
| Angelos Hatzakis | Commissioner | Greece |
| Natasha Martin | Commissioner | US |
| Sharon Hutchinson | Commissioner | UK |
| Shira Zelber-Sagi | Commissioner | Israel |
| Marieta Simonova | Commissioner | Bulgaria |
| Michael Ninburg | Commissioner | UK |
| Annalisa Belloni | Commissioner | UK |
| Esther Aspinall | Contributor | UK |
| Margaret Hellard | Contributor | Australia |
| Nick Scott | Contributor | Australia |

| WG 2 | Role | Country |
|---|---|---|
| Jeffrey V Lazarus | Chair | Spain |
| Tatjana Reic | Commissioner | Croatia |
| Michael Ninburg | Commissioner | UK |
| Patrizia Carrieri | Commissioner | France |
| Tim Rhodes | Commissioner | UK |
| Damon Barrett | Contributor | Sweden |
| Harry Rutter | Contributor | UK |
| Carla Treloar | Contributor | Australia |

| WG 3 | Role | Country |
|---|---|---|
| Rachel Pryke | Chair | UK |
| Phil Newsome | Commissioner | UK |
| Hannele Yki-Järvinen | Commissioner | Finland |
| Maria Buti | Commissioner | Spain |
| Angelos Hatzakis | Commissioner | Greece |
| Pere Gines | Commissioner | Spain |
| Tatjana Reic | Commissioner | Croatia |
| Shira Zelber-Sagi | Commissioner | Israel |
| Hanny Yeshua | Contributor | Israel |
| Mathews Mead | Contributor | UK |
| Isabel Graupera | Contributor | Spain |
| Christos Lionis | Contributor | Greece |
| Juan Mendive | Contributor | Spain |

| WG 4 | Role | Country |
|---|---|---|
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| Rachel Pryke | Commissioner | UK |
| Bruno Sangro | Commissioner | Spain |
| Phil Newsome | Commissioner | UK |
| Shira Zelber-Sagi | Commissioner | Israel |
| Michael Ninburg | Commissioner | UK |
| Tom Hemming Karlsen | Commissioner | Norway |
| Giulio Marchesini | Contributor | Italy |

| WG 5 | Role | Country |
|---|---|---|
| Phil Newsome | Chair | UK |
| Hannele Yki-Järvinen, | Commissioner | Finland |
| Shira Zelber-Sagi | Commissioner | Israel |
| Nick Sheron | Commissioner | UK |
| Elisabetta Bugianesi | Commissioner | Italy |
| Helena Cortez-Pinto | Commissioner | Portugal |
| Harry Rutter | Contributor | UK |

| WG 6 | Role | Country |
|---|---|---|
| Maria Buti | Chair | Spain |
| Natasha Martin | Commissioner | US |
| Marieta Simonova | Commissioner | Bulgaria |
| Michael Ninburg | Commissioner | UK |
| Angelos Hatzakis | Commissioner | Greece |
| Robert Flisiak | Commissioner | Poland |
| Tatjana Reic | Commissioner | Croatia |
| Geoff Dusheiko | Commissioner | UK |

| WG 7 | Role | Country |
|---|---|---|
| Deirdre Kelly | Chair | UK |
| Michael Manns | Commissioner | Germany |
| Tom Hemming Karlsen | Commissioner | Norway |
| Christoph Schramm | Contributor | Germany |
| Albert Pares | Contributor | Spain |
| Cyriel Ponsioen | Contributor | The Netherlands. |
| Alison Taylor | Contributor | UK |
| Ekkehard Sturm | Contributor | Germany |
| Henkjan Verkade | Contributor | The Netherlands |
| Claus Petersen | Contributor | Germany |

| WG 8 | Role | Country |
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| Vincenzo Mazzaferro | Chair | Italy |
| Patrizia Burra | Commissioner | Italy |
| Marieta Simonova | Commissioner | Bulgaria |
| Alessandro Cucchetti | Contributor | Italy |
| Philip Johnson | Contributor | UK |

| WG 9 | Role | Country |
|---|---|---|
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| Shira Zelber-Sagi | Commissioner | Israel |
| Patrizia Burra | Commissioner | Italy |
| Marina Maevskaya | Commissioner | Russia |
| Miquel Serra | Contributor | Switzerland |
| Elsa Solà | Contributor | Spain |
| Cristina Solé | Contributor | Spain |
| Isabela Graupera | Contributor | Spain |
| Elisa Pose | Contributor | Spain |
| Núria Fabrellas | Contributor | Spain |
| Laura Napoleone | Contributor | Spain |
| Adrià Juanola | Contributor | Spain |

## List of abbreviations

| | |
|---|---|
| **AFP** | Alpha fetoprotein |
| **AI** | Artificial Intelligence |
| **AIH** | Autoimmune hepatitis |
| **ALP** | Alkaline phosphatase |
| **ALT** | Alanine aminotransferase |
| **Anti-HCV** | Antibodies anti hepatitis C Virus |
| **APRI** | AST to platelet ratio index |
| **AST** | Aspartate aminotransferase |
| **AUC** | Area under the curve |
| **AUDIT-C** | Alcohol Use Disorders Identification Test |
| **AVMSD** | Audio-visual Media Services Directive |
| **BARDA** | Biomedical advanced research and development agency |
| **BMI** | Body Mass Index |
| **CCA** | Cholangiocarcinoma |
| **CCM** | Chronic care model |
| **CHE** | Switzerland |
| **CI** | Confidence Interval |
| **CLICK** | Comprehend the digital marketing environment, Landscape of campaigns, Investigate exposure, Capture on screen and Knowledge sharing |
| **COVID-19** | Coronavirus Disease 2019 |
| **CTLA-4** | Cytotoxic T-Lymphocyte Antigen -4 |
| **DAA** | Direct acting antivirals |
| **DALYs** | Disability Adjusted Life Years |
| **DILI** | Drug induced liver disease |
| **DNA** | Deoxyribonucleic acid |
| **DRG** | Diagnostic Related Grouping |
| **DVD** | Digital versatile discs |
| **EASL** | European Association for the Study of the Liver |
| **EEA** | European Economic Area |
| **e.g.** | Exempli gratia |
| **eGFR** | Estimated glomerular filtration rate |
| **ELF** | Enhanced Liver Fibrosis |
| **EPIC** | European Prospective Investigation into Cancer and Nutrition |
| **ERN RARE LIVER** | European Reference Network for Rare Liver Diseases |
| **EU** | European Union |
| **F1-4** | Fibrosis Grade 1-4 |
| **FIB-4** | FIB-4 fibrosis index |
| **FLI** | Fatty liver index |
| **GBD** | Global Burden of Disease |
| **GBR** | Great Britain |
| **GDPR** | General Data Protection Regulation |
| **GGT** | Gamma glutamyl transpeptidase |
| **GPs** | General practitioners |
| **HAV** | Hepatitis A virus |
| **HbA1c** | Hemoglobin A1c |

| | |
|---|---|
| **HBsAg** | Hepatitis B surface antigen |
| **HBV** | Hepatitis B virus |
| **HCC** | Hepatocellular carcinoma |
| **HCV** | Hepatitis C virus |
| **HDV** | Hepatitis D virus |
| **HERA** | European Health Emergency Response Authority |
| **HEV** | Hepatitis E virus |
| **HFSS** | High fat, sugar and salt foods |
| **HIV** | Human immunodeficiency virus |
| **IBD** | Inflammatory Bowel Disease |
| **ICD-10** | International classification of diseases |
| **ISL** | Israel |
| **IU/ml** | International Units per mililiter |
| **LBT** | Liver blood tests |
| **MAFLD** | metabolic dysfunction-associated fatty liver disease |
| **MDT** | Multi-disciplinary team |
| **MIR** | Mortality to incidence ratio |
| **MSM** | Men who have sex with men |
| **MUP** | Minimum pricing? |
| **NAFLD** | Non alcoholic fatty liver disease |
| **NASH** | Non alcoholic steatohepatitis |
| **NCD** | Non communicable diseases |
| **NICE** | National Institute for Clinical Excellence |
| **NSP** | Needle syringe programs |
| **NOR** | Norway |
| **ODHIN** | Optimising Delivery of Healthcare Intervention |
| **OECD** | Organisation for Economic Co-operation and Development |
| **OST** | Opiod substitution treatment |
| **PD1** | Programmed cell death protein 1 |
| **PSC** | Primary Sclerosing Cholangitis |
| **PWID** | People who inject drugs |
| **QALY'S** | Quality adjusted life years |
| **RNA** | Ribonucleic acide |
| **RUS** | Russian Federation |
| **SDG** | Sustainable Development Goal |
| **SLE** | serious liver events |
| **SPHeP-NCDs** | Strategic Public Health Planning for Non Communicable Diseases |
| **SSB** | Sugar sweetened beverages |
| **TNF** | Tumor Necrosis Factor |
| **TV** | Television |
| **UK** | United Kingdom |
| **UPF** | Ultra processed food |
| **US** | United States |
| **WHO** | World Health Organisation |

## Methods descriptions for display items

### *Table 1 methods*

The prevalence and incidence of cirrhosis (total, compensated and decompensated) are estimated in the Global Burden of Disease (GBD) study[2] using a compartmental model in the Disease modelling meta-regression (DisMod-MR) tool, version 2.1, with prevalence inputs from hospital and claims data, cause-specific mortality inputs from the GBD causes of death modeling process, excess mortality inputs modeled using the Meta-regression, Bayesian, Regularized Trimmed (MR-BRT) tool, and the Global Burden of Disease (GBD) suite of predictive covariates. The incidence of liver cancer is modeled from mortality-to-incidence ratios from cancer registries and mortality estimates from the GBD causes of death modeling process. The prevalence of liver cancer is then estimated from incidence estimates combined with survival information from the SEER database. The proportions of cirrhosis cases and liver cancer cases assigned to NAFLD are modeled using cirrhosis case-series data in DisMod-MR 2.1. The prevalence of NAFLD, in the absence of cirrhosis or liver cancer, is estimated in DisMod-MR using survey data. Years of life lost (YLLs) are calculated by first estimating cause-specific deaths for all age-groups using Causes of death ensemble modelling (CODEm) and CoDCorrect, and the deducting the age at death from a theoretical minimum risk life expectancy for all deaths, and summing. Detailed GBD results can be viewed (https://vizhub.healthdata.org/gbd-compare/) and downloaded (http://ghdx.healthdata.org/gbd-results-tool) from the IHME website, and detailed methods are described in (https://www.thelancet.com/cms/10.1016/S0140-6736(20)30925-9/attachment/deb36c39-0e91-4057-9594-cc60654cf57f/mmc1.pdf).

***Figure 1 methods***

Raw ICD-10 mortality data was last updated by the WHO in December 2019. These files were downloaded from https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/download-the-raw-data-files-of-the-who-mortality-database and analysed. CSV data was imported into SPSS where ICD-10 data was recoded and a sum table calculated before it was imported into Excel for plotting.

***Figure 2 methods***

Death counts for 23 age-groups, both sexes, 204 locations and 29 years were estimated for six leading causes of death (https://www.thelancet.com/cms/10.1016/S0140-6736(20)30925-9/attachment/deb36c39-0e91-4057-9594-cc60654cf57f/mmc1.pdf, see pages p215, p195, p270, p220, p345) using vital registration, verbal autopsy and cancer registry data (https://www.thelancet.com/cms/10.1016/S0140-6736(20)30925-9/attachment/deb36c39-0e91-4057-9594-cc60654cf57f/mmc1.pdf, see page p20), along with predictive covariates, in the Causes of death ensemble modelling (CODEm) algorithm (https://www.thelancet.com/cms/10.1016/S0140-6736(20)30925-9/attachment/deb36c39-0e91-4057-9594-cc60654cf57f/mmc1.pdf, see page p48) and CoDCorrect process (https://www.thelancet.com/cms/10.1016/S0140-6736(20)30925-9/attachment/deb36c39-0e91-4057-9594-cc60654cf57f/mmc1.pdf, see page p55). Years of life lost (YLLs) for each year-age-sex-location combination were calculated by subtracting age at death from the theoretical minimum risk life-expectancy and summing (https://www.thelancet.com/cms/10.1016/S0140-6736(20)30925-9/attachment/deb36c39-0e91-4057-9594-cc60654cf57f/mmc1.pdf, see page p56. For this figure, YLLs for deaths occurring in individuals aged 15-64

years old were summed across both sexes and all locations for each year 1990-2019. The figure was created in SPSS.

***Figure 3 methods***

Standardised death rates (SDR) for chronic liver disease and cirrhosis 1968 – 2016 categorised by country and year or death were downloaded as a CSV file from the WHO HFA explorer web site (https://gateway.euro.who.int/en/hfa-explorer/). The WHO HFA was last checked in March 2021 at which time the most recent SDR update remained from 2016. Data were imported into SPSS for analysis, plots were created for each country and the trajectory of liver SDR were graded by eye into one of five categories, low, decreasing, intermediate, increasing and very high. The figure was created in SPSS.

***Figure 5 methods***

Standardised mortality rates from chronic liver disease and mean alcohol consumption data (L/capita) were downloaded from the WHO-HFA online dataset https://gateway.euro.who.int/en/hfa-explorer/ for which data was last updated in 2016, categorised by country and year of death. Data was imported into SPSS and liver SDR / alcohol ratio calculated for each time point, data was visualised on a scatter plot of liver SMR v alcohol consumption but data were categorised according to the liver SMR / alcohol ratio (cut off = 4.0). This illustrates that while for most countries there is a relatively tight correlation between liver mortality and population level alcohol consumption, in a signifiant minority the liver mortality is either higher or lower compared with alcohol consumption. The figure panels were created in SPSS.

***Figure 6 methods***

Deaths due to liver cancer in the Global Burden of Disease (GBD) study[2] are estimated using data from vital registration, verbal autopsy and cancer registries, combined with predictive covariates using the Causes of death ensemble modelling (CODEm) approach. Cancer registry data with information on both incidence and mortality are used to model mortality-to-incidence ratios using Space-Time Gaussian Process Regression (ST-GPR) (https://www.thelancet.com/cms/10.1016/S0140-6736(20)30752-2/attachment/54711c7c-216e-485e-9943-8c6e25648e1e/mmc1.pdf see page p34), and these ratios are applied to mortality estimates from CODEm to produce incidence estimates. Survival is modeled from Surveillance, Epidemiology, and End Results (SEER) mortality-to-incidence ratio data using a generalized linear model with a quasi-binomial family and logit link, and survival estimates were combined with incidence estimates to produce prevalence estimates. The proportion of liver cancer cases attributable to NASH is estimated from published liver cancer case-series, modeled using the Disease Modelling Meta-regression (DisMod-MR 2.1) tool (https://www.thelancet.com/cms/10.1016/S0140-6736(20)30925-9/attachment/deb36c39-0e91-4057-9594-cc60654cf57f/mmc1.pdf; General cause of death data prep and modeling with CODEm page 20; and page 48 Cancer-specific cause of death modeling page 195; and Cancer incidence and prevalence modeling page 803; General DisMod page 459). In the past 30 years, the prevalence of liver cancer due to NASH has almost doubled (age standardized rates per 100,000). NASH-related liver cancer death rates and incidence rates have also increased in the past 3 decades.

***Figure 8 and 9 methods (also accounting for Supplementary Figures 4 and 5)***

See separate OECD Analysis Appendix section for details.

***Figure 10 methods***

See separate Viral Hepatitis Modelling Appendix section for details.

***Figure 13 methods***

The Health Behaviour in School-aged Children (HBSC) survey is a World Health Organization collaborative cross-sectional study conducted since 1983 in a growing number of countries across Europe and North America, but for the purpose of this analysis, only Europe region data were included (for detailed list of countries please see Table below).[3] Data collection procedures in all countries are conducted in accordance with a standardized international protocol.[4] Data are collected in school settings every 4 years from a nationally representative random cluster sample of the 11-, 13-, and 15-year-old adolescents in each participating country. The primary sampling unit is schools. More detailed information about the methodology of the HBSC study is reported elsewhere.[4]

Body mass index (BMI) (kilogram per square meter) was calculated using self-reported weight and height, and body weight status was assessed according to the International Obesity Task Force cut-off values in three categories[5]: underweight/ normal weight, overweight , and obesity.[6] Students were categorized into overweight or obese and not overweight or obese. All eating behaviors are reported in a structured questionnaire and responses were categorized into two categories: consumption on a daily basis (one or more per day) vs. lower non-daily consumption

and never. Socioeconomic status was assessed by the Family Affluence Scale (FAS), a reliable indicator of family wealth. The score obtained was recorded on a 3-point ordinal scale: low, medium, and high family affluence.[7] In this figure, only the low vs high categories are presented. Pearson Chi-Square was done to test differences in overweight and eating behaviors between affluence categories, all P values were significant <0.001.

*Countries/WHO region participating in the Health Behaviour in School-aged Children (HBSC) survey, included in the current Analysis**

| *Country/WHO region* | *N* |
|---|---|
| Albania | 1765 |
| Azerbaijan | 4586 |
| Austria | 4129 |
| Armenia | 4717 |
| Belgium (Flemish) | 4333 |
| Belgium (French) | 4020 |
| Bulgaria | 4548 |
| Croatia | 5169 |
| Czech Republic | 11564 |
| Denmark | 3181 |
| Estonia | 4725 |
| Finland | 3169 |
| France | 9173 |
| Georgia | 4242 |
| Germany | 4347 |
| Greece | 3863 |
| Hungary | 3789 |
| Iceland | 6996 |
| Ireland | 3833 |
| Israel | 7712 |
| Italy | 4144 |
| Kazakhstan | 4868 |
| Latvia | 4412 |
| Lithuania | 3797 |

| | |
|---|---|
| Luxembourg | 4070 |
| Malta | 2576 |
| Republic of Moldova | 4686 |
| Netherlands | 4698 |
| Norway | 3127 |
| Poland | 5224 |
| Portugal | 6126 |
| Romania | 4567 |
| Russia | 4281 |
| Serbia | 3933 |
| Slovakia | 4785 |
| Slovenia | 5667 |
| Spain | 4320 |
| Sweden | 4185 |
| Switzerland | 7510 |
| Ukraine | 6040 |
| Macedonia | 4658 |
| England | 3405 |
| Scotland | 5021 |
| Wales | 15951 |
| Total | 221912 |

*Canada and Greenland were excluded.

*Number of boys and girls with available data for each variable (and with available FAS)*

| *Variable* | *N boys* | *N girls* |
|---|---|---|
| Overweight/ obese | 82404 | 84008 |
| Fruits intake | 100485 | 103826 |
| Vegetables intake | 100076 | 103604 |
| Sweets intake | 100081 | 103612 |
| Soft drinks intake | 100154 | 103631 |

***Figure 14 methods***

**Inequality and Diabetes and Obesity among Persons aged 50–65 in Europe**

In order to examine the prevalence and patterns of diabetes and obesity in Europe, data from the Survey of Health, Aging and Retirement in Europe (SHARE) were analyzed. SHARE-Europe aims to better understand the dynamics of the growing population of persons aged 50+. In addition, it aims to provide a research infrastructure for public policymaking on behalf of the aging population. The data collected in SHARE offer a unique means by which to compare the health, economic situation, and welfare of older people in different European countries over time. SHARE is a multidisciplinary, cross-national bank of microdata on health, psychological and economic variables (http://www.share-project.org/home0.html).[8-11] We used the data gathered in the "wave" of SHARE in 2017. European countries with available data are included. People aged 50–65 in each of these countries were examined.

*Variables*

A person with diabetes was specified on the basis of two questions that were asked at each point of time in the survey: "Has a doctor ever told you that you had/do you currently have diabetes or high blood sugar?" and "Do you currently take drugs at least once a week for diabetes?" If the survey participant answered either question in the affirmative, he/she is defined as a "person with diabetes." Obesity definition was based on the calculation participant's body-mass index (BMI). Obesity is defined as a BMI of equal or above 30. Economic status definition was based on assessment of household

economic capacity (two situations: make ends meet with difficulty and make ends meet easily).

*Main findings*

The prevalence of diabetes is higher among those who report difficulty in their household's making ends meet versus those who report making ends meet easily. The prevalence of obesity is higher among those who report difficulty in making ends meet versus those whose households make ends meet easily. Both for diabetes and obesity, these differences persisted across all countries, and for diabetes there was about two-fold difference in several countries.

***Figure 15 methods***

Pseudo-anonymised data from University Hospitals Southampton 2004-2018 was imported into SPSS and hospital admission data merged with outpatient administration data.[12,13] The relationship between the first recorded admission with cirrhosis or liver failure and any preceding appointment at the liver clinic analysed. The time period between the liver clinic appointment and the subsequent first liver admission was categorised. A Cox regression survival analysis was performed to examine if these individuals had a reduced survival compared with patients given the opportunity for a liver clinic assessment.

| | | Alive | % | Dead | % |
|---|---|---|---|---|---|
| TimeOPcode | > 3 years | 97 | 5.3 | 49 | 3.2 |
| | 2-3 years | 43 | 2.4 | 19 | 1.2 |
| | 1-2 yrs | 79 | 4.3 | 39 | 2.5 |
| | 6-12 months | 76 | 4.2 | 48 | 3.1 |
| | 0-6 months | 347 | 19.1 | 188 | 12.2 |
| | no OP prior to first liver admission | 1175 | 64.7 | 1194 | 77.7 |
| | | 1817 | 100 | 1537 | 100.0 |

***Figure 16 methods***

Under an international collaboration,[14] data were accrued retrospectively from four different areas in Japan (Ogaki Municipal Hospital, Ogaki, Gifu; 2,599 patients), Hong-Kong (Chinese University of Hong Kong, Hong-Kong; 1112 patients), the United Kingdom (University of Birmingham, Birmingham and University of Newcastle, Newcastle; 1356 patients) and Spain (Universidad de Navarra, Pamplona; 834 patients). Patients of all disease stages and etiologies were included. Overall survival was plotted using the Kaplan-Meier method.

***Figure 19 methods***

Raw ICD-10 mortality data was last updated by the WHO in December 2019. These files were downloaded from https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/download-the-raw-data-files-of-the-who-mortality-database. Data on the price of alcohol (Price level Index) in Purchasing Power Parities 2007-2018 were downloaded from Eurostat https://ec.europa.eu/eurostat/web/main/data/database. Datasets were imported into SPSS and scatter plots created.

*Global Burden of Disease (GBD) 2019 summary*

The GBD data inputs and methodologies to produce all above estimates are described in detail in https://www.thelancet.com/cms/10.1016/S0140-6736(20)30925-9/attachment/deb36c39-0e91-4057-9594-cc60654cf57f/mmc1.pdf. In brief, death certificate, verbal autopsy and cancer registry data (https://www.thelancet.com/cms/10.1016/S0140-6736(20)30925-

9/attachment/deb36c39-0e91-4057-9594-cc60654cf57f/mmc1.pdf; see page 20) are combined with predictive covariates to model liver cancer mortality and cirrhosis mortality using the Causes of death ensemble modelling (CODEm) algorithm (see pages https://www.thelancet.com/cms/10.1016/S0140-6736(20)30925-9/attachment/deb36c39-0e91-4057-9594-cc60654cf57f/mmc1.pdf; see pages p48, p195, p270). GBD then assigns liver cancer and cirrhosis deaths to aetiologies based on proportions modeled from published case-series data (see https://www.thelancet.com/cms/10.1016/S0140-6736(20)30925-9/attachment/deb36c39-0e91-4057-9594-cc60654cf57f/mmc1.pdf; see pages p 270, p 894) using a Bayesian meta-regression tool called DisMod-MR 2.1 (see https://www.thelancet.com/cms/10.1016/S0140-6736(20)30925-9/attachment/deb36c39-0e91-4057-9594-cc60654cf57f/mmc1.pdf; see page 459 and Abraham D. Flaxman, Theo Vos, and Christopher J. L. Murray, An Integrative Metaregression Framework for Descriptive Epidemiology).

***Methods for Supplementary Box 1***

**Primary care surveys**

The EASL Lancet Liver Disease Commission Primary Care Working Group (PCWG) carried out two surveys. Firstly, a questionnaire developed by the PCWG was sent to a lead GP within each nation's main primary care organisation as listed through WONCA (https://www.woncaeurope.org/member-organisations to gauge a snapshot of primary care involvement in liver disease across Europe. Responses were received from 19 countries. The survey themes were collated by the PCWG chair and reviewed and agreed by the PCWG. Secondly, questionnaires were sent to individual GPs using a Survey Monkey format, to explore personal viewpoints of barriers and opportunities to how liver disease care could be improved.

*Survey questions*

The Lancet-EASL Commission on Liver Diseases in Europe is seeking to understand variation across European countries in how GPs provide and have access to testing and treatment of liver disease. There is little published data on primary care aspects of liver disease. We wish to understand barriers and opportunities for improving care.

| | Yes or No |
|---|---|
| **1.** Which country do you represent? _____ | |
| | |
| **2.** Has liver disease been recognised as a health priority for primary care in your country? | |
| a. Liver disease generally has been highlighted | |
| b. A specific aspect of liver disease has been highlighted, (eg Hepatitis infection, or alcohol related liver disease) | |
| c. Liver disease has <u>not</u> been recognised as a health priority | |
| Free text: | |
| | |
| **3.** Does liver disease care (testing and/or treatment) generate specific payment for GPs in your country or is it included in general workload/payment systems? Please indicated whether | |
| a. Specific payments are linked to aspects of liver disease care | |
| b. Liver disease does not generate any specific payments | |
| c. Other | |
| Free text: | |
| | |
| **4.** Is liver disease care well-coordinated between primary and secondary care in your country? E.g. recognised testing, management and referral pathways. Please indicate whether | |
| a. Generally well-coordinated across the country; | |
| b. Poorly or not coordinated | |
| c. Coordinated care may be found in some localities but is variable nation-wide | |
| d. Other | |
| Free text: | |
| | |
| Re testing: | |
| **5.** What tests do laboratories typically include in the standard liver panel or 'hepatic' panel? | |
| a. 'LFT' request will deliver full panel of liver blood tests including AST, ALT, ALP, bilirubin, GGT, AST/ALT ratio, albumin | |

| | |
|---|---|
| b. 'LFT' request will deliver a limited set of tests. Additional test requests must be specified separately | |
| c. GPs must specify individually which liver tests they require | |
| Free text: | |
| | |
| **6.** Is liver fibrosis testing accessible in your country? | |
| a. Typically only through referral to liver specialist/gastroenterologist | |
| b. Readily accessible to GPs using indirect fibrosis algorithms based on blood tests eg NAFLD fibrosis score; AST:ALT ratio; FIB4; APRI; | |
| c. Readily accessible to GPs using scanning e.g. transient elastography (Fibroscan) or ARFI | |
| d. Any/all of the above depending on regional variations | |
| Free text: | |
| | |
| **7.** Are GPs in your country encouraged to use a recognised pathway or guideline(s) to guide investigation of abnormal liver blood tests? Y or N | |
| Please name or describe any guidelines used if possible. | |
| Free text: | |
| | |
| **8.** Do patients in your country have access to state-funded risk-factor support for | |
| (Delete Yes or No as appropriate) | |

| | Face to face support | Web-based support |
|---|---|---|
| a. Obesity management | Yes No | Yes No |
| b. Alcohol dependence | Yes No | Yes No |
| c. Drug dependence | Yes No | Yes No |
| d. Physical activity engagement | Yes No | Yes No |

| | |
|---|---|
| Free text: | |
| | |
| **9.** GP Education and training (<u>not</u> undergraduate training) regarding liver disease is | |
| a. Mandated in curriculum and widely available | |
| b. Commonly accessible but entirely optional | |
| c. Not widely available / not easily accessible | |
| d. Unusual for GPs | |
| Free text: | |
| | |
| **10.** Please give any other comments that you feel are relevant regarding the status of or attitudes to liver disease in primary care in your country. E.g. how educational plans could address perceived need | |

*Key survey response themes*

1. Is LD recognised as a priority?
   ONLY 2 COUNTRIES HIGHLIGHTED LD GENERALLY
   12 COUNTRIES HAVE HIGHLIGHTED CERTAIN ASPECTS OF LD – TYPICALLY HEPATITIS C AND VACCINATION

*Comment: Examples show that leadership and prioritising LD as a clinical domain can help to develop services. UK is an example.*

Prioritising LD is challenging because the diverse array of liver disorders overlap with a wide variety of specialists. Investigation and monitoring using liver blood tests is widely undertaken independently of whether a differential diagnosis of liver disease is being considered.

| "Liver disease" Clinical domain | Commonly led through |
|---|---|
| Infectious disease | Public health/microbiology/hepatologist |
| Metabolic disease | General physician /hepatologist/diabetologist |
| Lifestyle-related disease | Primary care/public health/most clinical specialties |
| Autoimmune disease | Hepatologist/rheumatologist |
| Gallbladder-disease | Surgeon/gastroenterologist |
| Liver-related cancer | Oncologist/surgeon |

2. Are there any funding incentives to promote aspects of LD care?

   NO COUNTRIES REPORTED ALLOCATING SPECIFIC FUNDING TO ASPECTS OF LIVER DISEASE CARE. (E.G. NO QOF POINTS IN UK)

   *Comment: Exploration of incentivisation mechanisms to promote aspects of LD care should be more widely considered to drive engagement. Compare with other clinical domains that have had high profile in primary care e.g. CVD, where specific aspect of care has been nationally prioritised and coordinated, by setting standards and outcome goals. E.g. Karelia project Finland* https://www.who.int/chp/about/integrated_cd/index2.html

   *In UK the Quality and Outcomes Framework (QOF) incentivises GPs to improve care in specific clinical domains, which resulted in a significant changes in management of chronic kidney disease, but with variable impact on holistic care and other other health improvement indicators.* https://bjgp.org/content/67/664/e775 *No QOF points have been allocated for any aspects of liver disease. The effect of funding incentives is illustrated starkly where funding of a clinical domain is withdrawn at a later date with a resulting reduction in the incentivised healthcare intervention.* http://blogs.lshtm.ac.uk/prucomm/files/2018/07/QOF-Removal-report-2-July-2018-.pdf

3. Is there evidence that primary and secondary care are working together to provide coordinated LD care?
   13 COUNTRIES SAID POOR OR NO COORDINATION BETWEEN 1RY AND 2RY CARE, SOME REPORTING REGIONAL VARIATION, AND 6 COUNTRIES STATING THERE IS COORDINATION.

   *Comment: This appears to be a missed opportunity by specialist colleagues to lead, educate and partnership with primary care.*

4. Is a comprehensive panel of liver blood tests available to primary care?
   SIGNIFICANT VARIATION AROUND WHAT 'LFTS' MIGHT MEAN. 5 COUNTRIES SAID IT WOULD RESULT IN FULL ARRAY OF LIVER BLOOD TESTS, 5 REPORTED A LIMITED PANEL OF TESTS, AND 14 SAID IT WAS UP TO GPS TO CHOOSE SPECIFIC INDIVIDUAL TESTS. (There was some overlap with second option of limited panel)

   *Comment: -*

   1. *What should a 'standard liver panel' look like? Lack of uniformity around understanding of which liver blood tests are carried out or available will impact on the translatability of evidence across different countries. This also impacts on educational programmes:– what exactly are GPs expected to test? In what situations or at what thresholds should investigation be arranged? And, most importantly, do they have access to those tests? Is the guidance on how to interpret liver blood tests available and locally approved?*
   2. *It is important to consider the drivers of change: There is no point in guidelines advocating a plan of testing/treatment if those options are simply unavailable on the ground. Guideline recommendations must be combined with leadership and funding to ensure capacity and facilities are in place when education to broadcast new guidelines is disseminated. UK NICE NAFLD Guideline demonstrated the ineffectiveness of a poorly coordinated guideline which recommended a test (ELF) that is not readily available or commissioned.*
   3. *It is essential to understand how/why GPs request LFTs in usual practice. Disease-specific guidelines are not very useful for GPs because they are rarely faced with a clear diagnosis – GPs usually begin with diagnostic uncertainty and vague symptoms or mildly abnormal incidental findings. Main reasons for requesting LFTs include:-*
      a. *Monitoring of medication (eg statins, epilepsy medication ) or as part of monitoring other long-term conditions, eg CVD, DM [Common reason]*
      b. *Investigation of diagnostic uncertainty and unclear symptoms, such as weight loss, GI symptoms etc – i.e. 'pathology fishing trips' [Common reason]*
      c. *In response to abnormal liver investigation e.g. coincidental liver abnormality noted during ultrasound for unrelated issue. E.g. fatty liver finding during gynaecology scanning. [Increasingly common reason]*
      d. *Because of direct suspicion of liver disease, e.g. in a heavy drinker [Far less common reason]*

5. Is liver fibrosis testing accessible to primary care?
   ONLY 1 COUNTRY REPORTED READY WIDESPREAD ACCESS TO FIBROSIS SCANNING BY GPS. FIBROSIS TESTING REQUIRES

REFERRAL TO SPECIALIST IN 9 COUNTRIES, COULD BE ASSESSED USING ALGORITHMS IN 5 COUNTRIES AND 3 COUNTRIES REPORTED REGIONAL VARIATION (INCLUDING UK).
A free text comment (Poland) explained that "whilst algorithm calculation is feasible, there is no established practice to calculate fibrosis risk in primary care, nor clear pathway for further management of elevated scores or easy access to elastography. The assumption is therefore that such patients would be referred to a specialist."

*Comment: Much groundwork around investigating LFTs and developing guidelines and pathways needs to be done alongside pushing for any increase in fibrosis testing because it is essential that fibrosis testing forms part of a coordinated approach to managing LD across 1ry and 2ry care.*
*There is lack of consensus between hepatologists around what is the best test for fibrosis – how should GPs make sense of conflicting opinion? Where GPs have a confusing array of choices over tests the default option is to do nothing. Eg AST:ALT ratio, NAFLD fibrosis score, FIB4; APRI; ELF; Why would a GP know which one to go for? Guidance must be simple and specific if it is to be followed by busy non-specialists.*

6. Are clinical pathways for investigating and managing LD established?
CLINICAL PATHWAYS ARE NOT WELL-DEVELOPED. 11 RESPONDENTS STATED THERE IS NO RECOGNISED PATHWAY IN THEIR COUNTRY, WHILST 8 DESCRIBED AN ESTABLISHED PATHWAY EITHER ALREADY IN PLACE OR CURRENTLY IN DEVELOPMENT. ONE COUNTRY SAID OCCASIONALLY SOME CLINICIANS USE BSG GUIDELINES DUE TO HAVING NO NATIONAL GUIDELINE.
Guideline limitations: The Polish response described 2 Polish guidelines but lack of coordination to make those guidelines feasible on the ground:
"There are certain guidelines for the management of liver diseases in primary care but they generally do not take into account what testing is really available in general practice. In order to exclude HCV there is a need to refer patient to a specialist. Apart from LFTs, HBsAg and liver US no testing for specific liver disease such as autoimmune liver disease, Wilson disease, PBC, PSC is available in primary care"

*Comment: As stated above, developing pathways is not enough unless there is structured investment in putting in the testing and management infrastructure for the pathway to be feasible. The UK example of NICE guideline demonstrated that a high-level recommendation (ELF testing) has little impact if investment to provide access to ELF is not available in practice.*

7. Is state-funded LD risk factor support readily available in the community?
THERE IS PATCHY AVAILABILITY OF RISK-FACTOR SUPPORT SERVICES ACROSS EUROPE. ROUGHLY HALF OF COUNTRIES OFFER OBESITY FACE TO FACE SUPPORT OR WEB-BASED SUPPORT. A SLIGHTLY HIGHER PROPORTION OFFER FACE TO FACE ALCOHOL AND

DRUG DEPENDENCE SUPPORT (9 OUT OF 14 FOR EACH RISK FACTOR), BUT ONLY HALF OF COUNTRIES PROVIDING WEB-BASED SUPPORT. Some respondents did not answer this section. Fewer countries provide physical activity support with only 4 out of 14 countries providing this, whilst half of respondents offer web-based support for PA (although one respondent commented that this may be of questionable quality.)

*Comment: The benefits of investing in wider access to risk-factor support impact far more widely than just liver disease. Physical activity remains under-recognised as an impactful lifestyle intervention with limited investment in support services across Europe. The emerging evidence base of effective interventions for obesity also suggest that further investment would benefit LD outcomes. Putting in support services to address established risk factors for liver-disease should generate just as much effort as detecting LD – not much point detecting L disease if there is no support available to address it once it is recognised.*

8. Is LD included in primary care post-graduate training?
   11 COUNTRIES STATED THAT LD IS INCLUDED IN MANDATORY POSTGRADUATE TRAINING OR IS AT LEAST READILY AVAILABLE. 4 COUNTRIES DESCRIBED THAT EDUCATION IN LD IS NOT EASILY AVAILABLE OR IS UNUSUAL FOR GPS.
   *When considering educational programmes, it is vital to achieve some consensus over what is to be taught. Ideally, establishing pathways, addressing access to testing and considering how elements of work should be funded would be better carried out <u>before</u> developing educational programmes.*

### *Methods for Supplementary Box 2*

Members of WG8 (V.M., A.C., P.J., B.S.) designed a survey that collected data regarding the participant's level of involvement in the treatment of liver cancer patients, specialty, availability of a Multidisciplinary Team (MDT) in the participant's working centre, number and type of patients discussed by the MDT, extent of non-application of MDT recommendation, pattern of referral to other centres (for physician's not directly involved in the care of liver cancer patients), and the participant's opinion about how patient sex or ethnicity can influence the therapeutic choice in their clinical practice. It was created as an electronic survey on the web-based survey platform Google Forms and was publicized by EASL through the

website and email listings. No incentives or honorarium were provided for completion of the survey. Participants were not identified by any means.

The responses to the survey questions were analysed to generate numerical and graphical summaries. For categorical variables, frequencies and percentages were used.

Survey Part A

*What is your work*

A. I am a physician directly involved in the treatment of liver cancer patients (hepatocellular carcinoma and/or intrahepatic/hilar cholangiocarcinoma) in a hospital setting.
B. I am a physician who participates in the management of liver cancer patients in a non-hospital setting and refers patients for therapy elsewhere.
C. I am not a physician, or I am a physician but not involved in the management of liver cancer patients

For those choosing options A or B

1. What is your specialty?

- Hepatologist
- Gastroenterologist
- Surgeon
- Medical Oncologist
- Radiation Oncologist
- Radiologist
- Nuclear Medicine Specialist
- Pathologist

- Nurse

2. In your hospital, is there a Multidisciplinary Team (MDT) that meets regularly to provide advice in the management of liver cancer patients?

- Yes
- No or not regularly

3. How many patients are discussed at MDT?

- Almost every patient (>80%)
- Not all patients (50-80%)
- Some patients (<50%)
- No MDT in my Hospital

4. What kind of patients did you discuss?

- Every single patient
- Only cases where the diagnosis and/or the therapy to adopt is uncertain or eventually outside recommended guidelines
- Me and/or my team take therapeutic decisions

5. How often is the recommendation from the MDT not followed?

- Almost never (>90% of compliance)
- Occasionally (50-90% of compliance)
- Frequently (<50% of compliance)

<u>For those choosing option C</u>

6. Where do you refer patients suffering with liver cancers?

- To a hospital with an MDT which manages liver cancer
- Directly to some colleagues who are expert in liver cancer treatment

Survey Part B

What is your opinion in regard to patients suffering from liver cancer you observe in your clinical practice?

7. Do you feel that patient sex can influence the therapeutic choice?

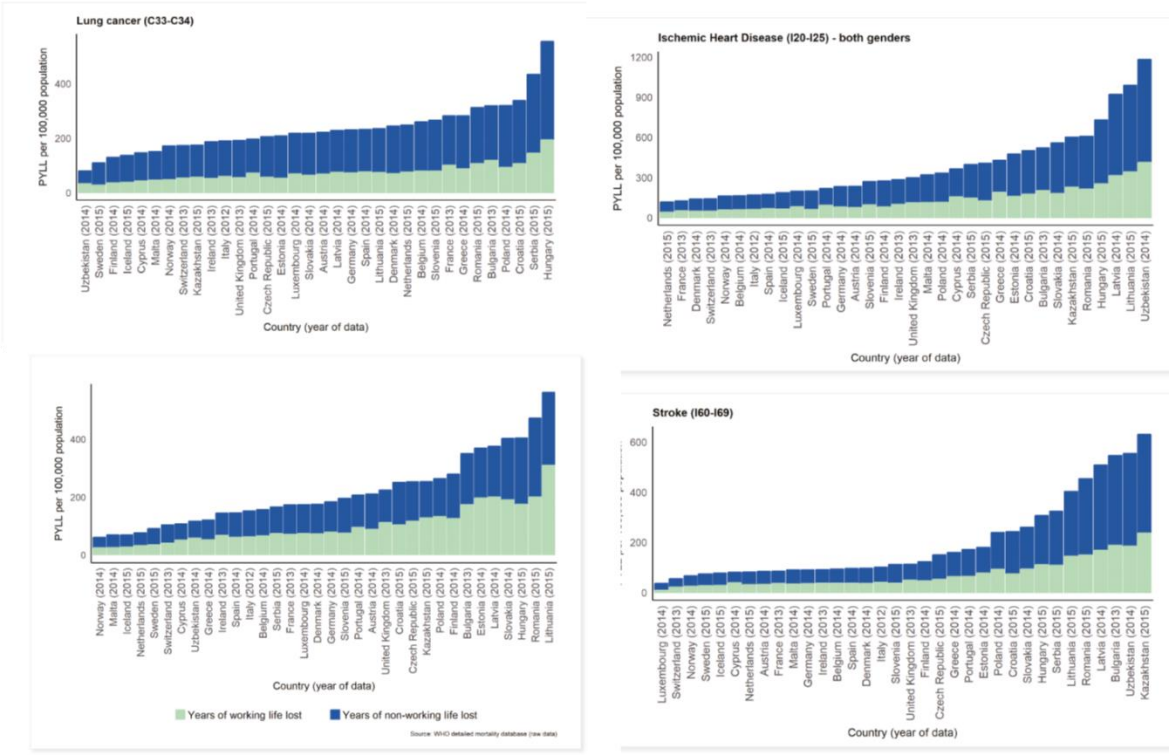
- (choice of 5 levels from *almost surely NO* to *almost surely YES*)

8. Do you feel that patient ethnicity can influence the therapeutic choice?

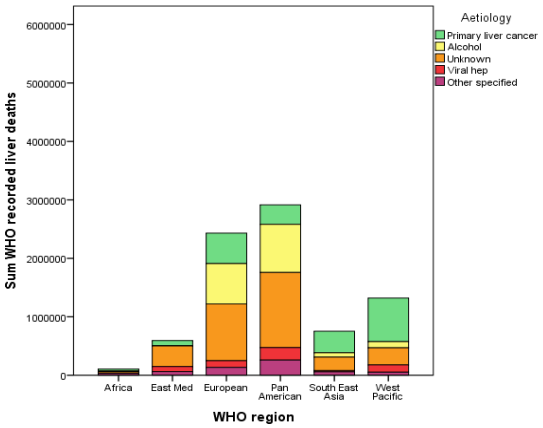
- (choice of 5 levels from *almost surely NO* to *almost surely YES*)

## Supplementary Figures

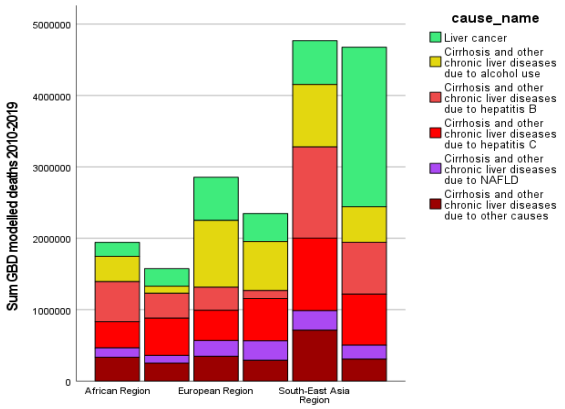
**Supplementary Figure 1.** Age-standardised potential years of life lost (working and non-working) for all lung cancer, ischemic heart disease, all liver diseases and stroke – both genders in most recent year (reprinted with permission from the HEPAHEALTH report - https://easl.eu/publication/hepahealth-project-report/).



**Supplementary Figure 2**. Panel A. Most recently available raw ICD-10 data on global liver mortality (2010-2016) is recorded from death certification processes by the WHO and subsequently remodeled. Panel B Most recently available comparison from the Global Burden of Disease study (2010-2019). Note that GBD also ascribes an aetiology to primary liver cancer, but these aetiologies have been combined to facilitate comparison with the WHO data, which does not provide an aetiology for primary liver cancer. GBD models utilize death certificate, verbal autopsy and cancer registry data (https://www.thelancet.com/cms/10.1016/S0140-6736(20)30925-9/attachment/deb36c39-0e91-4057-9594-cc60654cf57f/mmc1.pdf; see page 20, along with predictive covariates, to model liver cancer mortality and cirrhosis mortality using the Causes of death ensemble modelling (CODEm) algorithm (https://www.thelancet.com/cms/10.1016/S0140-6736(20)30925-9/attachment/deb36c39-0e91-4057-9594-cc60654cf57f/mmc1.pdf; see pages p48, p195 and p270). GBD then assigns liver cancer and cirrhosis deaths to aetiologies based on proportions modeled from published case-series data (https://www.thelancet.com/cms/10.1016/S0140-6736(20)30925-9/attachment/deb36c39-0e91-4057-9594-cc60654cf57f/mmc1.pdf; see pages p270 and p894).




**Panel A**



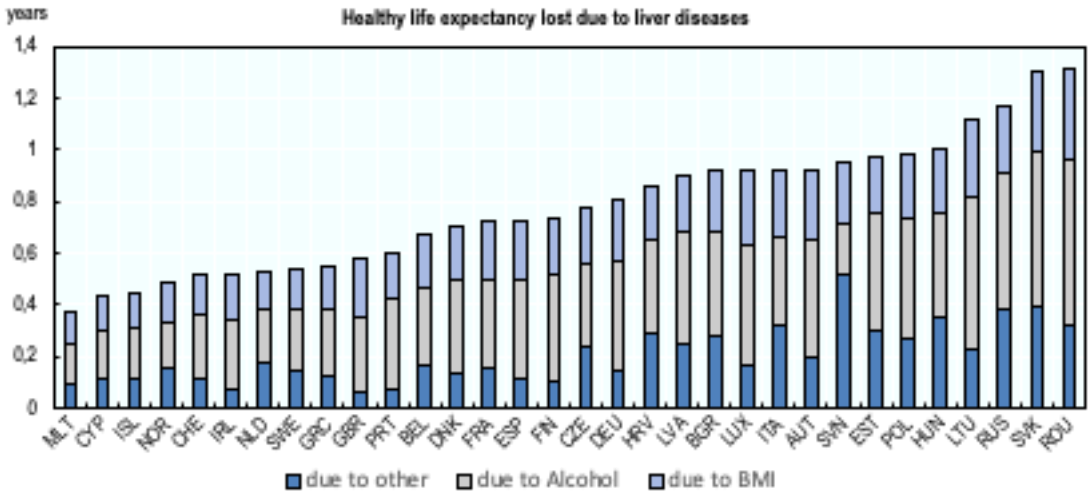

**Panel B**

**Supplementary Figure 3.** There has been a directly inverse relationship between life expectancy and alcohol consumption in Russia where a panoply of effective alcohol measures has resulted in dramatic improvements in life expectancy, clearly showing the benefits of this approach. Figure is reproduced with permission from the WHO case study authors.[15]

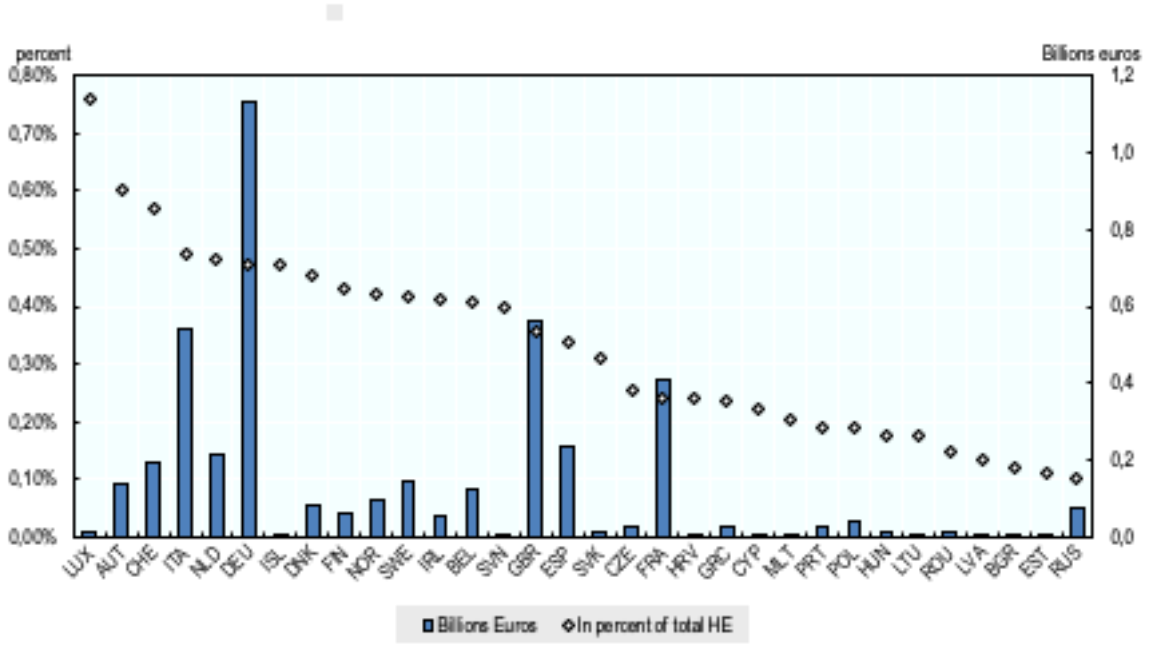
Fig. 12. Relationship between alcohol consumption and life expectancy[a]


[a] Left scale: life expectancy in years.
Right scale: total alcohol consumption per capita in litres.
*Source: Global status report on alcohol and health, 2018;*[24] Manthey et al. (2019);[25] Federal State Statistics Service.[20]
Adapted from Nemtsov, Neufeld & Rehm (2019).[37]

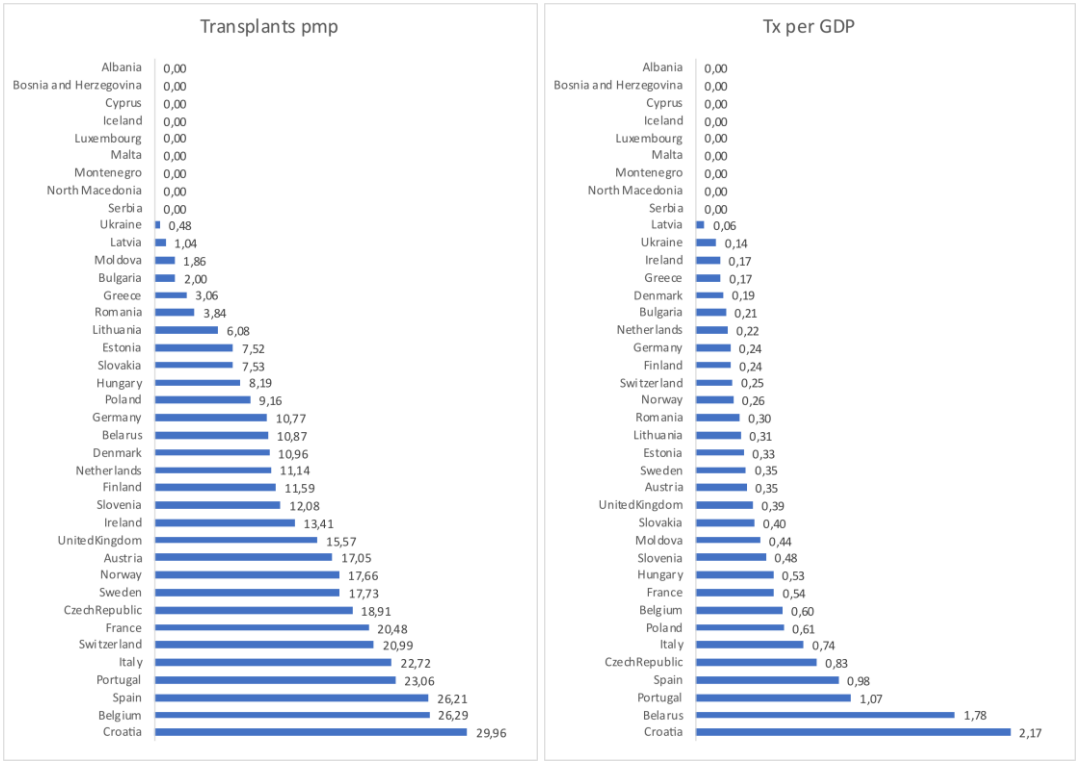
**Supplementary Figure 4.** Annual loss of healthy life expectancy in years due to liver disease according to aetiology, calculated by the OECD Strategic Public Health Planning for non-communicable diseases (SPHeP-NCDs) model. For further details, see Supplementary Methods.



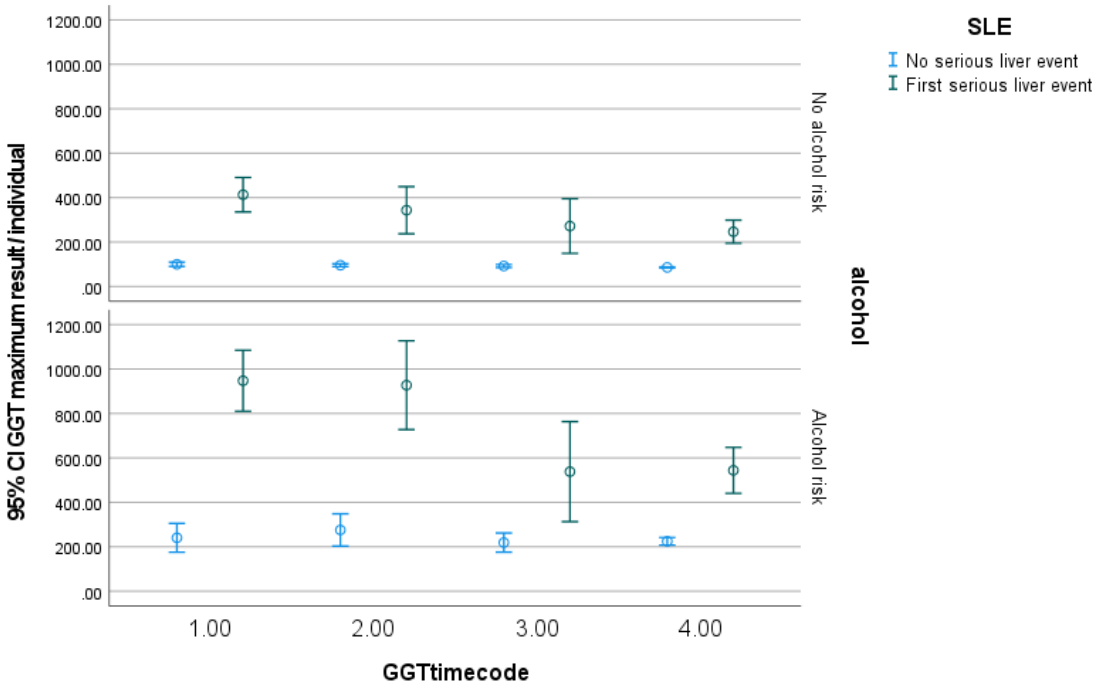
**Supplementary Figure 5.** The economic cost of liver disease in the EU 27+5 in billions of Euro or as a percentage of total health expenditure calculated by the OECD Strategic Public Health Planning for non-communicable diseases (SPHeP-NCDs) model. For further details, see Supplementary Methods.



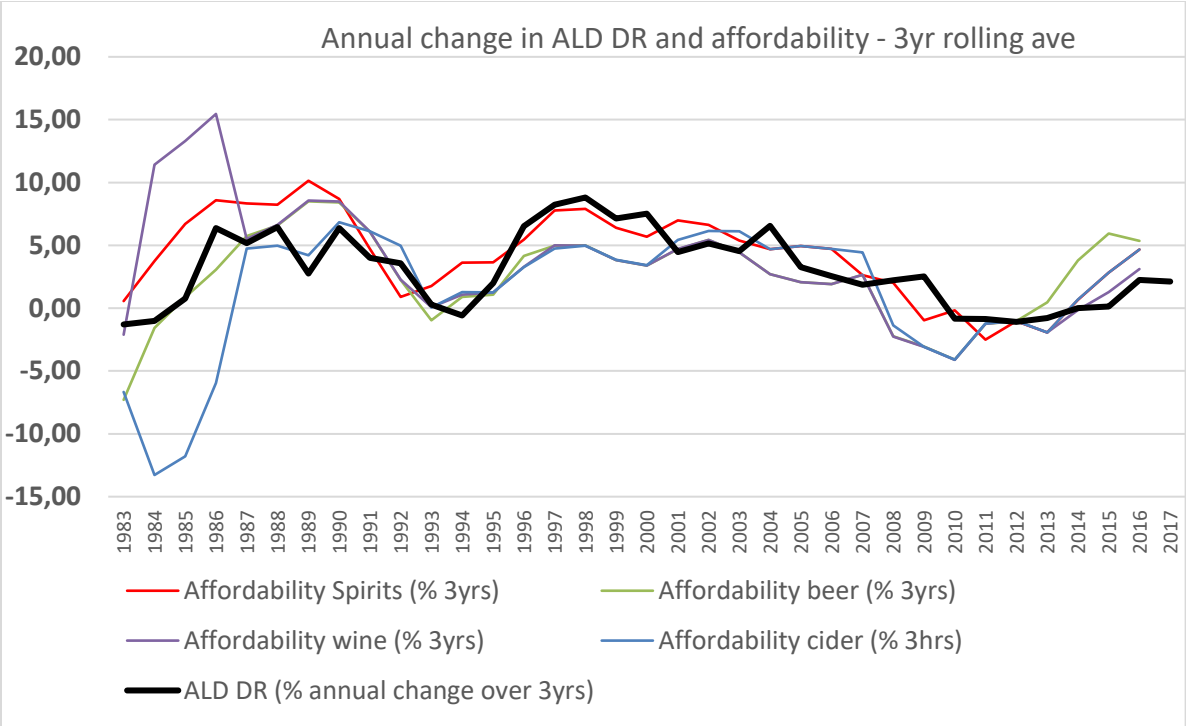
**Supplementary Figure 6**. Liver transplants per population (million people and year) and per gross domestic product (GDP; thousand US dollars per person). Data calculated based on data from the European Liver Transplant Registry (www.eltr.org).



**Supplementary Figure 7.** Gamma-glutamyl transferase (GGT) data were available in 41,829 subjects in the CIRRUS dataset[12] of whom 1,565 subsequently suffered a first liver event, GGT levels were elevated by alcohol and type diabetes, but were substantially higher in patients who went on to have a first liver event. As a result the prediction cut offs for an serious liver event (SLE) were as follows; No risk factors 79 IU, Type 2 diabetes 82 IU, Alcohol risk 126 IU, respectively.



**Supplementary Figure 8.** Relationship between UK liver deaths rates and the affordability of different alcohol beverages. Average (mean) annual % change over 3 rolling year periods to smooth data. Data from Office for National Statistics (ONS) and the UK government (Her Majesty's Revenue and Customs, HMRC); analysis by NS. ALD DR; alcohol-related liver disease death rates.



## Supplementary Tables

**Supplementary Table 1.** European archetypes of liver health. Experience transfer opportunities exist between low/decreasing and high/increasing groups of countries, and systems to facilitate this learning opportunity must be implemented at an European level. Categories are derived from **Figure 2**.

| |
|---|
| **Low**: Cyprus, Iceland, Israel, Montenegro, Netherlands, Norway, Sweden, Turkey |
| **Decreasing**: Austria, Belgium, Bosnia and Herzegovina, Switzerland, Denmark, Spain, France, Georgia, Greece, Italy, Luxembourg, Malta, Portugal, Serbia, Slovenia |
| **Intermediate**: Albania, Azerbaijan, Czechia, Germany, Croatia, Hungary, Ireland, Lithuania, Latvia, Poland, Slovakia |
| **Increasing**: Armenia, Bulgaria, Belarus, Estonia, Finland, United Kingdom |
| **Very high**: Kazakhstan, Kyrgyzstan, Republic of Moldova, Romania, Tajikistan, Turkmenistan, Ukraine, Uzbekistan |

**Supplementary Table 2.** Comparison of Global burden of disease (GBD) and Office for National Statistics (ONS) data (source of WHO data) for liver related mortality. Data was extracted from the GDB results tool (http://ghdx.healthdata.org/gbd-results-tool. The GBD data refers to deaths from cirrhosis and chronic liver disease due alcohol use, hepatitis B, hepatitis C, non-alcohol-related fatty liver disease (NAFLD) and "other causes". Data are for England and Wales, 2019. ONS data was extracted from the NOMIS dataset (https://www.nomisweb.co.uk/query/construct/submit.asp?menuopt=201&subcomp=) . The ONS data is categorised by 4 figure ICD 10 codes. Of these liver deaths 474 deaths were attributed to specified diseases and 2,282 due to "unspecified causes". Data are for England and Wales, 2019, analysis by N.S..

| | **Liver related mortality 2019 ONS and GBD data** | | |
|---|---|---|---|
| **Aetiology** | **GBD E&W 2019** | **ONS NOMIS E&W 2019** | **GBD/ONS ratio** |
| Alcohol related liver disease | 4,602 | 4946 | 0.93 |
| Viral hepatitis | 1,201 | 165 | 7.28 |
| NAFLD | 948 | 669 | 1.42 |
| Other specified | 1,789 | 474 | |
| Other not specified | | 2282 | |
| Total | 8,540 | 8536 | 1.00 |

**Supplementary Table 3.** Commonly used algorithms for liver fibrosis assessment,[16,17] their test requirements and limitations for adoption in primary care. Hepatologists need to provide simplified advice as to choice of algorithm for primary care appication, hence the recommendation to use FIB-4, despite inherent limitations. BMI, body mass index; LBT, liver blood test; GGT, Gamma-Glutamyl Transferase; NAFLD, non-alcohol-related fatty liver disease; IR, insulin resistance; AST, aspartate transaminase; ALT, alanine aminotransferase; HCV, hepatitis C virus infection; MCV, mean corpuscular volume; INR, international normalized ratio.

| **Algorithm** | **Tests required** | **Limitations for primary care** |
|---|---|---|
| Fatty Liver Index | BMI, waist circumference, triglycerides and GGT | Triglycerides require a fasting blood sample – organisationally more costly.<br>GGT is not standard LBT |
| NAFLD Fibrosis Score** | Age, BMI, IR/diabetes, AST, ALT, Platelets, albumin | Repeat blood test needed |
| FIB4 | Age, platelet count, AST and ALT | Repeat blood test may be needed unless AST is part of routine LBT |
| APRI | AST, platelets | Repeat blood test may be needed unless AST is part of routine LBT |
| eLIFT | Age, gender, AST, GGT, Platelets, Prothrombin | Repeat blood test may be needed unless AST and prothrombin is part of routine LBT |
| CIRRUS | Albumin, bilirubin, sodium, creatinine, MCV, platelets | Prediction of first serious liver event, uses routine data, no special tests required |
| Forns index | Age, platelet count, GGT, cholesterol | HCV-oriented |
| Fibrosis Probability Index | Age, AST, cholesterol, past alcohol use, IR | HCV-oriented |
| Lok index | Platelet count, AST, ALT, INR | HCV-oriented |
| GUCI | Platelet count, AST, prothrombin, INR | HCV-oriented |
| Fibroindex | Platelet count, AST, GGT | HCV-oriented |
| Virahep-C model | Age, race, AST, platelet count, ALP | HCV-oriented |
| Hui score | BMI, bilirubin, albumin, platelet count | HCV-oriented |
| Bard score | BMI, diabetes, AST, ALT | NAFLD-oriented |

**Supplementary Table 4.** Minimal components in first step liver disease (liver blood tests, LBTs) assessment that also allows the calculation of FIB-4. As full blood count (FBC) is handled separately by haematology, its inclusion on this list is a recommendation to the clinician, whereas we propose the LBT panel is adopted as a default set of bloods when LBTs are requested. GGT, Gamma-Glutamyl Transferase; AST, aspartate transaminase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

| *Test* | *Purpose within the standardized LBT* |
|---|---|
| AST | inflammation and calculate fibrosis risk |
| ALT | inflammation and calculate fibrosis risk |
| ALP | bile duct obstruction and other<br><br>cholestatic liver diseases |
| bilirubin | bile duct obstruction, liver failure |
| albumin | liver failure / other clinical indications |
| FBC | Platelet count to calculate fibrosis risk |

## Supplementary Boxes

**Supplementary Box 1.** Feasibility of engaging general practicioners (GPs) in new work related to liver disease testing and follow-up. For details on underlying survey data, see Supplementary Methods.

| GPs will | GPs will mot |
|---|---|
| • Do what they are paid to do per reimbursement<br>• Do what is practically achievable<br>• Respond to patient demand<br>• Engage in multidisciplinary working and shared-care schemes | • Act if guidance or specialist advice is conflicting or unclear<br>• Absorb more unfunded work when they have no capacity for additional work<br>• Carry out tests that they don't have access to<br>• Take on responsibility that is beyond their training or contract |

**Supplementary Box 2.** To better understand the performance of liver cancer multidisciplinary teams (MDTs) in Europe we conducted a survey that was publicized through the European Association for the Study of the Liver (EASL) mailing lists and website, and responded by a total of 188 experts (see Supplementary Methods for details). Ninety per cent of respondents were physicians directly involved in the treatment of liver cancer patients in a hospital setting, as opposed to 10% of physicians who participate in the management of liver cancer patients in a non-hospital setting and refers patients for therapy elsewhere. The former were mainly hepatologists (74%) or gastroenterologists (14%), followed by surgeons (7%), radiologists (2%) and other specialists. There was no MDT in 5% of the respondents' centres and it did not meet regularly in another 6%. Where the MDT met regularly, almost every case (>80%) was only presented in 81% of centres, while not all cases (50-80%) and some cases (<50%) were discussed in 13.5% and 5.5%, respectively. Overall, respondents pointed out that every patient was discussed in 70% of centres; only those cases where the diagnosis and/or the therapy to adopt is uncertain or eventually outside recommended guidelines in 23% of centres; and therapeutic decisions were made by individual physicians in charge of the patient in 7%. The proportions among respondents working in a centre with a dedicated liver cancer MDT were slightly higher at 74.5%, 19.5% and 6%, respectively.

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## OECD Analaysis Appendix. Applications of the OECD SPHeP-NCD model in the EASL-Lancet Commission on Liver Disease in Europe

OECD's Strategic Public Health Planning for non-communicable diseases (SPHeP-NCDs) is a dynamic microsimulation model[1]. The model includes more than 26 diseases and 6 risk factors, representing the vast majority of the burden of disease. For this analysis, the modules on alcohol consumption, personal weight, liver cirrhosis and liver cancer, are those of highest interest. The model is used to quantify the impact of the risk factors and diseases as well as of prevention policies to promote healthier lifestyles consisting in lower levels of alcohol consumption and a heathier diet.

The microsimulation model consists of three core types of modules – a demographic, risk factor and disease modules. The demographic module assigns each individual in the model a birth date, gender and migration status. This is designed to create synthetic life histories (i.e. from birth to death), which, when aggregated, reproduce population dynamics for a given country, reflecting statistics in the United Nations' World Population Prospects[2].

Personal weight is modelled using a value reflecting the body-mass index (BMI) and is expressed as a continuous variable with a cumulative distribution function, ranging from 15 $kg/m^2$ to 150 $kg/m^2$. In this risk factor module, individuals are permanently allocated to a fixed quantile, with a higher quantile representing a higher level of BMI. Data on country-specific BMI distributions by gender and age are obtained from NCD RISC dataset[3].

The alcohol consumption module is designed to capture both the volume of alcohol consumption, expressed in grams of pure alcohol per day and the pattern of drinking (i.e. regular drinker, binge drinker and individual with alcohol use disorders). Individuals

are allocated to a fixed quantile representing their position in the distribution of alcohol consumption. Allocation to a pattern of alcohol consumption is based on a second fixed quantile distribution, which is calculated based on the volume of alcohol consumption and conditional probabilities derived from national datasets[4,5]. Both the volume and the pattern of alcohol consumption are used to classify individuals in the following categories: lifetime abstainer, current abstainer, moderate drinker (less than 40 grams per day for men and 20 grams for women of pure alcohol), heavy drinker (between 40 and 60 grams per day for men, and 20 and 40 grams for women of pure alcohol), and harmful drinker (more than 60 grams per day for men and 40 grams for women of pure alcohol). The modelling of alcohol consumption relies on two datasets: the IHME dataset[6] and the WHO Global Information System on Alcohol and Health[7].

Based on the characteristics assigned within the demographic and risk factor modules, an individual has a certain risk (i.e. relative risk) of developing a disease, such as liver cirrhosis or liver cancer, each year. Relative risks are based on those outlined in Global Burden of Disease study[8,9].

Finally, the disease module simulates the disease pathway (incidence, fatality and remission) through events at the individual level. For liver cancers, incidence and mortality data are computed using the Institute for Health Metrics and Evaluation (IHME) data, which is broken down by age, gender and year[9]. Remissions are calibrated to complement the number of deaths against incident cases in a five-year timeline – i.e. individuals who do not die from cancer within five years of being diagnosed are considered to have recovered. In practice, for each incident case, the person is assigned a probability of dying of cancer within five years and, in the case of a predicted death, a time to death based on mortality data. Cancer deaths do not occur uniformly within the five-year timeline from diagnosis, instead, using data from the

International Agency for Research on Cancer[10], each year is assigned a weight to reflect the fact that mortality is highest in the first year after diagnosis and declines thereafter.

Liver cirrhosis is modelled on two different levels: compensated cirrhosis and decompensated cirrhosis. Initially, individuals develop compensated cirrhosis, which may then become uncompensated. Individuals can die due to cirrhosis only if they have uncompensated cirrhosis. It is also assumed that there is no remission for cirrhosis. IHME data[8,9] is used to model transition rates (i.e. incidence rates) through the various levels and the fatality rate for decompensated cirrhosis. In addition, liver cirrhosis (both compensated and decompensated) is a risk factor for developing liver cancer, with literature suggesting that around 50% of people developing a liver cancer have cirrhosis[11]. The relative risk of developing a liver cancer with cirrhosis was estimated using the prevalence of cirrhosis (compensated and decompensated) and the incidence of liver cancer. A calibration of the resulting relative risk was carried out using the model-produced proportion of liver cancers in patients with cirrhosis to meet the 50% statistic.

For each year, the model produces a cross-sectional representation of the population, which is used to calculate health and economic outcomes associated with a scenario. The health outcomes include indicators such as life expectancy, disease prevalence and disability-adjusted life years (DALYs) using disability weights. Following the WHO definition, premature mortality is calculated as the number of deaths due to non-communicable diseases in the population aged 30 to 70[12]. The economic outcomes calculate the healthcare costs of disease treatment based on a per-case annual cost basis, which is extrapolated from national health-related expenditure data. The additional cost of multimorbidity is also calculated and applied[1]. Labour force

productivity is quantified by multiplying the numbers of days lost due to a non-communicable disease in the working-age population, as calculated by the OECD SPHeP-NCD model, and the average country-specific salary retrieved from ILOSTAT[13].

The model is designed to assess the impact of different scenarios: the burden of disease, consisting in the absence of a specific risk factor or diseases, or the implementation of an intervention. The impact of the scenarios is evaluated by comparing the counterfactual situation (i.e. the scenario) against a 'business-as-usual', which consists in a scenario in which no new intervention is introduced and provision of preventive and healthcare services remains at current levels specific to a country. The counterfactual scenarios are implemented in the model by modifying the input parameters to reflect the alternative scenario. Specifically, the burden of disease is evaluated by 'switching off' a disease or risk factor module, while policy interventions are modelled based on available evidence, usually from systematic reviews and meta-analyses.

Seven public health interventions were included in the analysis. Modelling the impact of individual public health interventions requires four inputs: 1) a description of the target population, including age group and health status; 2) exposure of the target population to the intervention; 3) effectiveness of the intervention at the individual level; and 4) time to maximum effectiveness and effectiveness over time. Input values for each of the primary prevention interventions evaluated in this study are summarized in **Table 1**, which have been sourced from the academic literature.

**Table 1.** Inputs to model: Selected public health interventions targeting alcohol consumption and unhealthy diet

| | Alcohol taxation | Alcohol Minimum unit price | Alcohol counselling | Ban on alcohol advertising to children | Restriction on alcohol opening hours | Food labelling | Food reformulation |
|---|---|---|---|---|---|---|---|
| Target age | all | all | all | <18 | all | >5 | All |
| Exposure | 100% | 100% | 20% | 90% | 40-99% | 15% | All |
| Effectiveness | 10% price increase reduces consumption by: 4% to 7% | Alcohol consumption: -0.6% to -3.3% | Alcohol consumption: -42 g/week (men), -30 g/week (women) | Underage drinking: -35%; Probability of dependence: -30% | Assault injuries: -34%; Traffic injuries: -1.5% | 0.40% lower BMI | -20% in calorie intake from food high in sugar, salt, calories and saturated fats |

A brief description of each intervention and the evidence used to model the intervention follows.

**Alcohol taxation** is an intervention assuming a 10% increase in the price of all alcoholic beverages due to an increase in the tax rate. Given inputs for the model were based on studies estimating the impact of taxes on consumption, as opposed to sales, estimates for this intervention take into account consumption of alcohol from illicit sources. Price elasticities for alcohol were derived from a systematic review and meta-analysis[14] and estimated along three dimensions: type of beverage; age of drinkers; and category of drinking. This information was then combined with the level of alcohol consumption per capita in each country.

**Minimum unit pricing (MUP):** this intervention sets a mandatory floor price per unit of alcohol or standard drink thereby targeting cheap alcohol beverages[15]. The intervention is modelled using three dimensions: a) the proportion of alcoholic beverages on the market that fall below a set minimum price threshold; b) the average price increase, per unit of alcohol, for beverages in the low-cost category; and c) the impact the price increase has on alcohol consumption[16,17].

**Alcohol counselling in primary care:** this intervention consists of detecting patients at risk for heavy drinking when they visit a general practitioner, and of delivering brief counselling about the alcohol-related harms and ways to reduce alcohol consumption. The programme targets hazardous and harmful drinkers (regular or episodic), excluding individuals dependent on alcohol, aged 18-70. The scenario assumes a reduction in alcohol consumption in the targeted individuals during the course of the intervention[18]. The impact of the intervention starts to decrease linearly after the end of the interventions and any impact disappears after 5 years[19,20].

**Ban on alcohol advertising to children**: the intervention sets a statutory and comprehensive ban on alcohol advertising targeting children. The intervention targets underage individuals to limit all the forms of marketing (e.g. including on social media). The intervention is modelled using two dimensions: a) reduction in the probability of drinking initiations in individuals aged 17 or below[21]; and b) reduction in the probability of dependence, based on evidence that people starting to drink after the legal drinking age have a risk of dependence 30% lower than those who drink while underage[22].

**Restrictions on outlet opening hours**: entailing restrictions in on-premise outlet opening hours, leading to a two-hour reduction. This policy was assumed to target the most densely populated areas of the countries concerned, corresponding to medium-sized and large cities. The policy scenario also involves increased enforcement efforts

by the relevant licensing and law enforcement authorities. Most of the impact of this policy is mediated by reduction in assault-related[23] and traffic-related[24] injuries.

**Food labelling:** the intervention models the impact of statutory measures requiring manufacturers or retailers to provide information on the nutritional composition of foods sold in supermarkets and other stores[25]. The intervention takes into account that not all calories consumed come from foods purchased in supermarkets and stores[26,27] and assumes that only a share of consumers will use the label to make decisions on what product to purchase.

**Food reformulation:** this intervention simulates the impact of the 20% calorie reduction for the foods in the relevant categories (i.e. high in sugar, salt, calories and saturated fats) proposed by Public Health England[28]. This reduction is implemented as a scenario requiring the implementation of different actions such as the establishment of partnerships to address the technical, social and policy issues arising throughout this effort. Some of the policies that countries have put in place to promote food reformulation include food labelling and menu labelling, mass media campaigns, changes in portion sizes, price policies targeting nutrient content above a certain threshold (e.g. sugar content), incentives for research and development.

The analysis assumes interventions are implemented in 2020, with results expressed over the period 2020-2050. Thirty-seven countries have been included in the analysis, which were chosen based on data availability. Given the model uses a standardized approach, the analysis allows for cross-country comparisons.

Detailed information on the OECD SPHeP-NCD model is available online at http://oecdpublichealthexplorer.org/ncd-doc/[1]. Detailed information on interventions to

promote healthier diets can be found elsewhere[29] as well as detailed information on interventions to tackle harmful alcohol consumption[14].

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# VIRAL HEPATITIS C ECONOMIC MODELLING for the EASL Lancet Commission on Liver Disease in Europe

## AIMS

For the European WHO region, we estimated the impact, total cost, cost-effectiveness and return on investment of scaling up hepatitis C prevention[1], testing and treatment (2020-2030) to achieve the WHO elimination targets of an 80% reduction in annual hepatitis C incidence and a 65% reduction in annual hepatitis C-related mortality by 2030[1], compared to 2015 levels.

For the elimination scenario, we have estimated (compared to the status-quo):

1) The reduction in hepatitis C prevalence, new infections and deaths
2) The cost of hepatitis C prevention, testing, treatment and disease management
3) The economic productivity gains associated with lower rates of absenteeism (hepatitis C-related sick days) and presenteeism (people being less productive as a result of their illness), and fewer premature deaths
4) The net economic benefit over time, including the year that it would become cost-saving.

[1] Harm reduction among people who inject drugs (PWIDs) was scaled up over a 5-year period (2020-2025) to reach WHO recommended levels (needle and syringe program [NSP] coverage was increased from an estimated 11% to 50% and opioid substitution therapy [OST] coverage was increased from an estimated 12% to 40% (Table 2)).

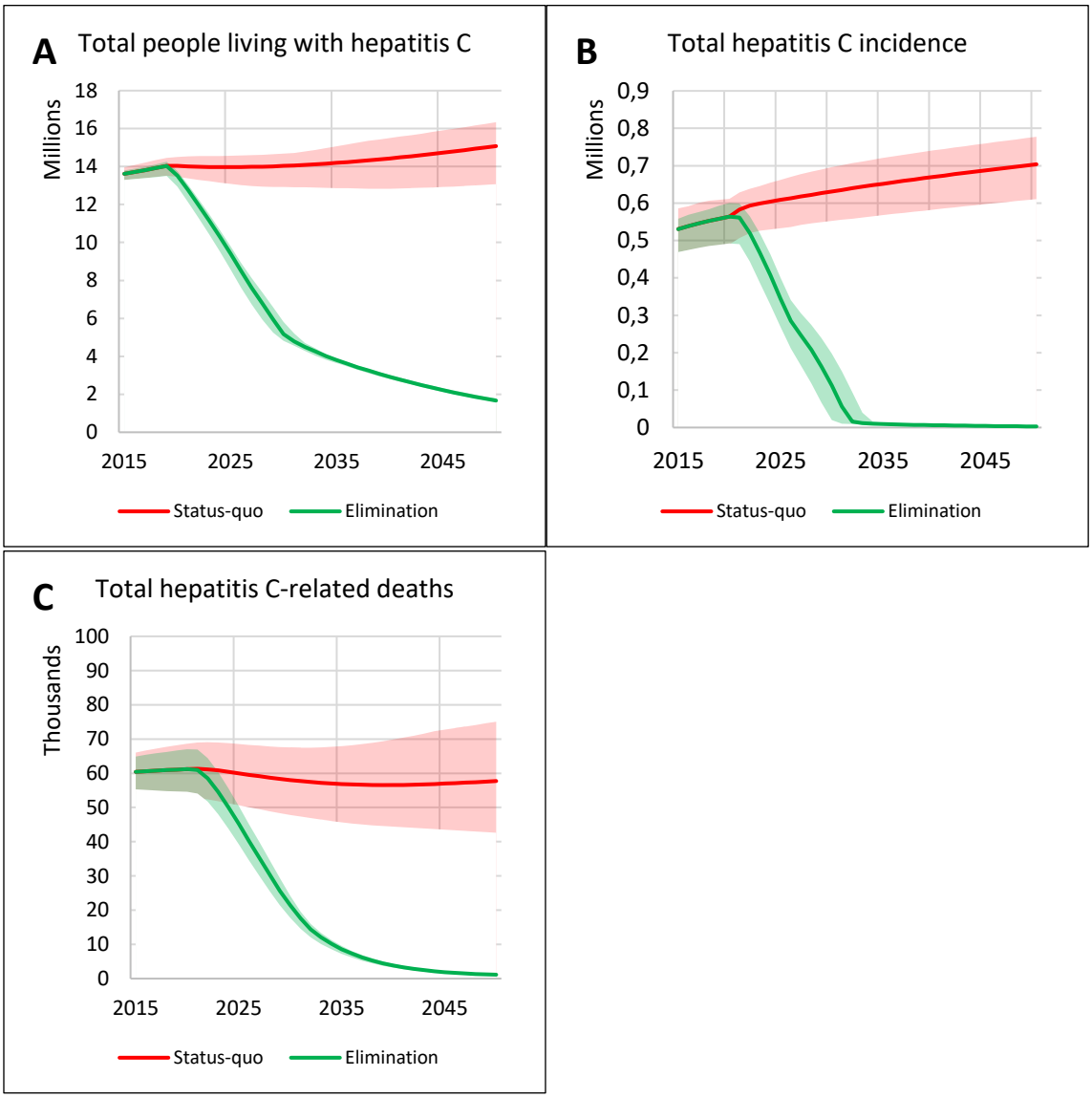


**Figure 1: Estimated impact of the elimination investment scenario in the WHO European region.** Projections for: the number of people living with hepatitis C (A), hepatitis C incidence (B), hepatitis C mortality (C). Solid line and shading represents median and interquartile range of multiple uncertainty simulations.

Table 1: Projected outcomes for the status-quo and elimination scenarios

| Outcome | Status-quo scenario | Elimination scenario |
|---|---|---|
| People with hepatitis C in 2030 | 14,032,000 (12,919,000 - 14,684,000) | 5,178,000 (4,820,000 - 5,813,000) |
| Hepatitis C incidence in 2030 | 631,000 (552,000 - 696,000) | 113,000 (20,000 - 197,000) |
| Hepatitis C-related mortality in 2030 | 58,000 (48,000 - 68,000) | 21,000 (18,000 - 24,000) |
| Cumulative incidence 2020-2030 | 6,662,000 (5,830,000 - 7,258,000) | 3,879,000 (2,993,000 - 4,504,000) |
| Cumulative mortality 2020-2030 | 659,000 (556,000 - 753,000) | 483,000 (421,000 - 538,000) |
| **Cumulative** direct costs 2020-2030 (prevention, testing, treatment, healthcare), billion euros | €20.08 (€18.27 - €21.80) | €53.24 (€47.91 - €56.50) |
| *Testing* | €3.93 (20%) (€3.73 - €4.19) | €15.04 (28%) (€13.23 - €15.99) |
| *Treatment* | €4.91 (24%) (€4.67 - €5.15) | €17.76 (33%) (€16.11 - €18.50) |
| *Healthcare* | €7.36 (37%) (€6.19 - €8.40) | €5.81 (11%) (€4.76 - €6.73) |
| *Harm reduction* | €3.88 (19%) (€3.68 - €4.08) | €14.63 (27%) (€13.81 - €15.28) |
| Cumulative direct costs 2020-2030 (excluding prevention), billion euros | €16.20 (€14.59 - €17.73) | €38.61 (€34.09 - €41.22) |
| Cumulative productivity losses (2020-2030), billion euros | €122.75 (€113.95 - €129.79) | €108.81 (€101.28 - €113.55) |
| *Absenteeism and presenteeism* | €90.86 (€86.68 - €93.72) | €80.92 (€76.65 - €82.80) |
| *Premature deaths* | €31.89 (€27.27 - €36.06) | €27.89 (€24.63 - €30.75) |
| Cumulative productivity losses (2020-2050), billion euros | €306.22 (€276.71 - €331.39) | €201.62 (€186.38 - €212.17) |
| *Absenteeism and presenteeism* | €207.72 (€195.12 - €216.39) | €148.20 (€139.71 - €153.01) |
| *Premature deaths* | €98.50 (€81.59 - €115.00) | €53.42 (€46.67 - €59.15) |
| Total DALYs 2020-2030 | 13,689,000 (11,870,000 - 15,327,000) | 9,696,000 (8,541,000 - 10,684,000) |
| Cost per DALY at 2030 from health systems perspective (testing, treatment, and healthcare costs; excluding productivity gains) | | €5,614 (€3,476 - €8,325) |
| **Net economic benefit at 2050** (difference in testing, treatment, healthcare and productivity losses), billion euros | | €94.97 (€84.34 - €111.87) |
| Including prevention costs | | |
| Cost per DALY at 2030 from health systems perspective | | €8,305 (€5,405 - €12,118) |
| **Net economic benefit at 2050** (billion euros) | | €68.88 (€57.12 - €87.25) |

## MODEL OVERVIEW

A mathematical model of hepatitis C transmission, disease progression and treatment was calibrated to the epidemic in the WHO European region based on previous modelling work[2,3]. Figure 2 schematically represents the structure of the model.

The number of people in each population group (people who inject drugs [PWID], former PWID, other) was tracked according to infection status (susceptible, acutely infected, and chronically infected) and stage of liver disease. The model also accounted for patients' progression through the hepatitis C care cascade: hepatitis C-infected individuals were classified as either undiagnosed, diagnosed hepatitis C antibody positive, diagnosed hepatitis C RNA positive, currently in treatment, or cured. Additional mortality risks were included for individuals with decompensated cirrhosis (DC) or hepatocellular carcinoma (HCC), and following cure progression from compensated cirrhosis to DC or HCC was still possible, but with a reduced risk. PWID were further classified by NSP status and OST status (dichotomously as covered or not covered), with those who were covered having a reduced probability of infection. Parameters and sources are provided in Table 2.

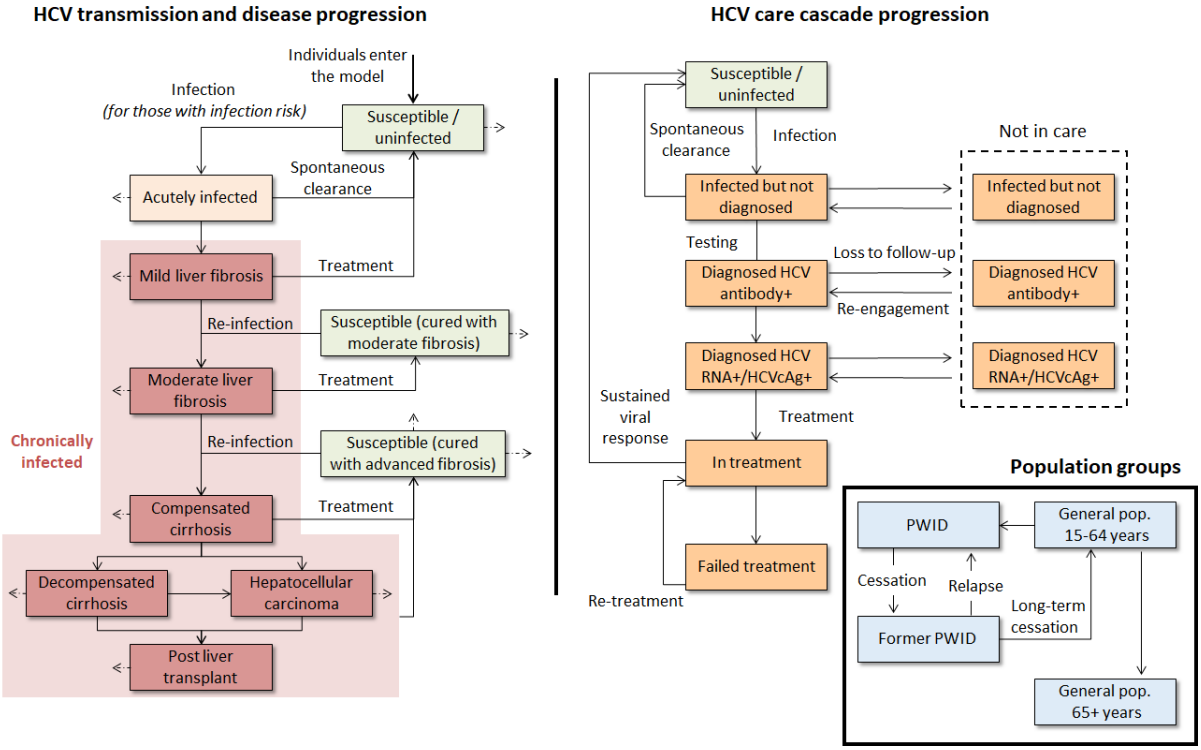


**Figure 2: model schematic.**

Table 2: Parameter estimates associated with model

| Variables | Value | Sources |
|---|---|---|

| *Costs* | | |
|---|---|---|
| Population-weighted per capita gross domestic product for WHO European region | €22,250 | Country estimates from the World Bank[4]. Population-weighted averages used to obtain estimates (US$25,200) |
| Ab testing | €30.24 | Commodity cost: US$23.30 (Honeycutt et al.[5]). US$1=€0.89.<br>Staffing cost: €9.51, based on one hour of provider time, with average salary calculated as the population-weighted per capita gross domestic product (GDP)[4] across Europe (per capita GDP inflated to account for unemployment). Assumes providers work 7 hours per day, 5 days per week and 45 weeks per year. |
| RNA testing | €71.81 | Commodity cost: US$70 (Xpert® HCV RNA test[6-8])<br>Staffing cost: €9.51, based on one hour of provider time. |
| Treatment | €2038.02 | Commodity cost: €2000 (assumed).<br>Staffing cost: €38.02, based on two hours of provider time |
| Fraction of human resource costs included for testing and treatment interactions | 50% | Assuming half can be absorbed within universal health care[9]. Only commodity costs applied to remaining interactions. |
| NSP | €78.24 | Platt et al.[10] Chapter 4 Table 8.<br>https://www.ncbi.nlm.nih.gov/books/NBK453605/table/table8/?report=objectonly<br>Pounds per syringe calculated by dividing the total cost by total # syringes (£0.36). Then multiplied by 200 (WHO coverage target) as an estimated average cost per PWID per year. £1 = €1.08. |
| OST | €1115.20 | Kenworthy et al.[11] UK study: methadone drug costs + dispensing costs + maintenance therapy costs = £1032.59 per year. £1 = €1.08. |
| Disease management costs (per patient per year)<br>*F0-2*<br>*F3*<br>*F4*<br>*DC* | <br>€97<br>€200<br>€233<br>€2,585 | WHO hepC calculator tool[12], with country-specific estimates used to generate population-weighted averages for the WHO European region (US$97, US$200, US$233, US$2585 and US$4754 for F0-2, F3, F4, DC and HCC respectively). |

| | | |
|---|---|---|
| *HCC* | €4,754 | |
| Fraction of disease management costs considered<br>*Undiagnosed*<br>*Diagnosed*<br>*Cured* | <br>25% of DC/HCC<br>25% of all disease<br>25% of DC/HCC | Uncertainty range 0-50%. Assumption, see methodology text. |
| Discounting | 3% per annum | |
| *Coverage and impact* | | |
| Treatments per year | Pre-2016: 89,000.<br>2016-2030 (status-quo): 271,000 | Polaris observatory[13] |
| Baseline harm reduction coverage<br>*NSP*<br>*OST* | <br>11%<br>12% | Larney et al.[14], Table 10.1 in appendix, aggregated values for European countries where data was available.<br>For NSP, total PWID covered was estimated as total syringes distributed / 200 (WHO coverage target per PWID). |
| Scaled up harm reduction coverage<br>*NSP*<br>*OST* | <br>50%<br>40% | Kelly et al.[15] estimated maximal NSP coverage among PWID in Europe.<br>WHO, UNODC, UNAIDS Technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users[16] |
| Treatment effectiveness | 95% | [17-20] |
| Relative incidence reduction on OST | 50% | 2018 Cochrane Review [21]; risk ratios for HCV acquisition 0.50 and 0.24 for OST and NSP (European estimate) respectively. No specific combined estimate was used (interventions implemented as independent reductions in force of infection for fraction covered). |
| Relative incidence reduction on NSP | 76% | |
| *Disutility weights* | | |
| F0-2 | 0.012 | No GBD estimate for F0-4, so used disability weights from Martin et al. [22]: for F0-2 and F3-4 used value for mild and moderate abdominopelvic problem [23] respectively, assuming linear disability increase from |
| F3-4 | 0.068 | |

| | | |
|---|---|---|
| | | mild chronic HCV to compensated cirrhosis (in line with other estimates [24]). |
| DC | 0.194 | Disability weights used in the Global Burden of Disease study[25] |
| HCC | 0.508 | |
| *Annual transition probabilities* | | |
| F0→F1 | 10.4-13.0% | Thein et al. [26]. Rates are calibrated between bounds to fit the distribution of liver disease and mortality over time. |
| F1→F2 | 7.5-9.6% | |
| F2→F3 | 10.9-13.3% | |
| F3→F4 | 10.4-12.9% | |
| F4→DC | 3.0-9.2% | National Centre in HIV Epidemiology and Clinical Research [27]. Rates are calibrated between bounds to fit the distribution of liver disease and mortality over time. |
| F4→HCC | 0.9%-3.8% | |
| DC→HCC | 4.1-9.9% | |
| DC→death | 7.4-20.2% | |
| HCC→death | 54.5-67.6% | |
| F4→DC (post cure) | 74% reduced risk | Nahon et al. [28], hazard ratio = 0.26 (0.17-0.39) |
| DC→HCC (post cure) | 71% reduced risk | Nahon et al. [28], hazard ratio = 0.29 (0.13-0.43) |
| DC→death (post cure) | 73% reduced risk | Nahon et al. [28], hazard ratio = 0.27 (0.18-0.42) for overall mortality following SVR for patents with cirrhosis. |
| HCC→death (post cure) | 73% reduced risk | |
| Spontaneous clearance probability | 26% | Micallef et al.[29] |
| *Region-specific characteristics* | | |
| 15-64 year old population size | 491 million | UN Population Division[30] |
| PWID population size | 1.82 million | United Nations Office on Drugs and Crime (UNODC) World Drug reports[31] |
| Hepatitis C-related mortality | 62,120 (in 2016) | WHO disease burden and mortality estimates (2000-2016)[32] |
| Hepatitis C antibody prevalence among PWID | 65% | Region specific, Nelson et al.[33] (population-weighted country averages used to obtain regional estimates). |
| Hepatitis C antibody prevalence in general population | 2.43% | Region specific, Gower et al.[34] (population-weighted country averages used to obtain WHO European region estimate). |
| Proportion of people living with hepatitis C who have cirrhosis | Calibrated | Calibrated to fit mortality data from the Global Burden of Disease study[35] (available data on cirrhosis could not |

| | | |
|---|---|---|
| | | be used as it estimated a greater number of cirrhotic patients than the total people living with hepatitis C) |
| Annual probability of being diagnosed | Calibrated | Calibrated to achieve the estimated proportion diagnosed in 2015 |

## MODEL CALIBRATION

A Particle Swarm Optimization Algorithm was used to best fit multiple model parameters to multiple epidemiological data points. The model was calibrated to time series data on the prevalence of hepatitis C among PWID, the prevalence of hepatitis C among the general population, the annual number of hepatitis C-related deaths, the total number of people living with hepatitis C, the estimated incidence of hepatitis C, and the proportion of people living with hepatitis C who were diagnosed. This involved simultaneously varying parameters for: the force of infection among PWID (the force of infection was dynamic and dependent on prevalence, but a constant scalar factor was varied), the disease progression rates (F0→F1, F1→F2, F3→F4, F4→DC, F4→HCC, DC→HCC), the annual probability of dying from DC, the annual probability of dying from HCC, and the annual probability of being diagnosed.

Due to some general population transmission (i.e. non-injection drug use related) occurring, to achieve consistency between regional-level data on incidence, prevalence and the total people living with hepatitis C it was also necessary to allow the estimated number of PWID and the average duration of injecting career to vary in the calibration procedure. This was done in place of directly modelling transmission among the general population, since it is not clear what fraction of the general population is at risk and for how long, and what proportion of new infections are attributable to general population transmission compared to injecting drug use. As a result, the PWID population group should be interpreted more generally as an “average risk population” for transmission each region.

## TESTING AND TREATMENT SCALE-UP

A baseline projection was conducted where prevention, testing and treatment was maintained at 2016 levels, with treatments (pre and post 2016) assumed to be prioritised towards to people with liver disease stage F3 or worse.

While the proportion of people with hepatitis C who were diagnosed was available, data on the total number of antibody and PCR tests were unavailable, and so the efficiency of testing to diagnose people (test positivity rate) was unable to be directly estimated. Therefore, hepatitis C antibody testing efficiency was estimated based on the prevalence in the populations being tested. For PWID, it was based on prevalence (i.e. in a 50% prevalence risk group it would require on average two tests to obtain one positive, assuming testing guidelines recommend screening of this group), while for the general population, testing was assumed to be conducted twice as well as random selection (i.e. if the general population prevalence was approximately 1%, this implies that it would require 50 tests to obtain one positive result). It was assumed that every three hepatitis C RNA tests among people diagnosed antibody positive resulted in one positive result, based on approximately a 25% spontaneous clearance rate. Following cure or Ab+/RNA- diagnosis, RNA tests were used for re-screening and positivity rates were decreased accordingly.

An optimisation was used to calculate the minimum budget, and budget allocation across antibody testing, RNA testing and treatment until the incidence and mortality targets were reached by 2030.

Testing and treatment were targeted to population groups in the model according to the following priorities: (1) people with liver disease stage F3 or worse to prevent deaths; (2) key transmission risk populations to prevent new infections; and (3) the rest of the general population with liver disease stages F0-2. A prevalence-based testing efficiency was maintained. Scale up of testing and treatment was assumed to begin in 2020.

## COST ESTIMATION

The direct hepatitis C costs of each scenario were calculated by adding the costs of testing and treatment (Table 2) to the costs associated with disease management (Table 2, by disease stage). Costs were discounted at a rate of 3%.

Data were unavailable on the staffing and infrastructure costs associated with scaling up testing and treatment. To account for staffing costs, it was assumed that each testing interaction required one hour of provider time and each treatment required a cumulative two hours of provider time (including overhead time), with population-weighted average per capita gross domestic product used as a proxy for providers' wages (Table 2). Infrastructure costs were excluded, as infrastructure was considered to become increasingly available with the Sustainable Development Goals universal healthcare coverage target. Our projections assumed that half of the human resource requirements for testing and treatment activities could be absorbed by staff in the context of universal health care (meaning that only 50% of interactions incurred staffing costs); however, given the simplicity of testing and treatment, it is possible that adequate human resources would already be available for all of these services. Therefore, our uncertainty analysis considered between 0-50% of staffing costs included.

It is unclear what fraction of people may remain engaged in care and incur disease management costs. The point estimate projections were based on disease management costs being applied to all diagnosed people (from all liver disease stages), all undiagnosed people with DC or HCC, and all cured people with DC or HCC.

## HARM REDUCTION

An average harm reduction coverage was estimated for the WHO European region based on Larney et al.[14] Average OST coverage was calculated as total PWID on OST in the countries reported divided by the estimated total PWID in those countries. NSP coverage was reported in total needles distributed per year, which was divided by 200 to convert to a proxy estimate for number of PWID sufficiently covered in the region (according to the WHO target of 200 needles per PWID per year).

In the elimination scenario, OST and NSP were scaled up over a five-year period (2020-2025) to 40% and 50% coverage respectively, with the impact, cost estimation and cost-effectiveness steps described above repeated. These scaled up harm reduction values were based on the WHO, UNODC, and UNAIDS technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users[16] (OST) and estimated maximal NSP coverage among PWID in Europe[15] (Table 2).

## PRODUCTIVITY GAINS

### Productivity gains from people cured of hepatitis C

The model calculated hepatitis C-attributable productivity losses due to absenteeism (due to a reduced workforce or from individuals working reduced hours), and presenteeism (where individuals are less productive at work due to their illness) (Figure 3). The model accounted for differential employment opportunities among PWID (former PWID were assumed to have the same parameters as all other non-PWID), as well as differential productivity and treatment uptake by cirrhosis status. The human capital approach[36] was used to estimate years of potential productive life lost, which were converted to economic outcomes using population-weighted average per capita gross domestic product. Total productivity losses were compared between the investment scenarios and the status-quo to determine economic gains. Parameters and sources are provided in Table 3.

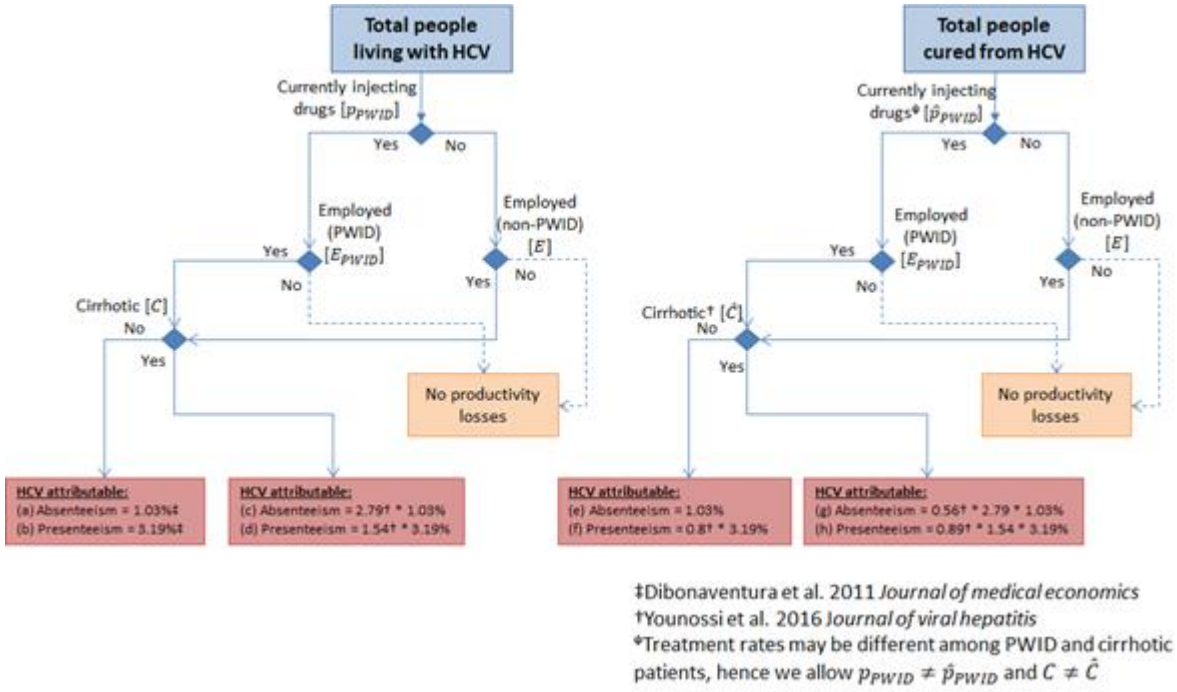


**Figure 3: schematic of productivity model**

### Productivity gains from averted deaths

Productivity gains from deaths averted were included. Total deaths averted in a given year were taken from the epidemic model projections; however a disproportionate amount of hepatitis C-related deaths are estimated to occur among older age groups (Table 3 shows the estimated 2016 age distribution of hepatitis C-related deaths[32]), and therefore only a fraction of these averted deaths were assumed to result in years of productive life gained. For each year in the projection timeframe (2020-2050), the productive life gained from deaths averted in that year were calculated by assuming:

- The fraction of averted deaths among the 60+ age category did not produce additional years of productivity
- Of the fraction of averted deaths among the 50-59 age category:
    - All of them contributed an additional year of productivity in the year they occurred;
    - 8/9$^{th}$ of these deaths contributed an additional year of productivity the year after they occurred (approximating 1/9$^{th}$ of this age band entering non-productive life at 60 years)

- 7/9$^{th}$ of these deaths contributed an additional year of productivity two years after they occurred;
- And so on, with the fraction of deaths averted from this age category contributing decreasing productivity gains for the next 9 years, before no longer producing additional productive years.

- Of the fraction of averted deaths among the 30-49 age category, the methodology above was used to attribute their ongoing productive years following the year that their death was prevented.

Years of productive life lost due to premature death were converted to economic outcomes using population-weighted average per capita gross domestic product.

Future economic productivity gains were discounted at 3%.

## NET ECONOMIC BENEFITS OVER TIME

The return on investment in year *t* was calculated as the difference in total (cumulative) direct costs (prevention, testing, treatment, disease management) plus the cumulative productivity gains:

*Cumulative status-quo direct costs (2020–t) – cumulative investment direct costs (2020–t) + cumulative productivity gains (2020–t)*

Table 3: Estimates of productivity losses due to hepatitis C infection and productivity gains resulting from treating hepatitis C infection

| Variables | Value | Source / comments |
|---|---|---|
| Region-specific parameters | | |
| Total people living with hepatitis C | 11.29 million (in 2013) | Country specific general population prevalence was taken from Gower et al.[34] Population-weighted averages used to obtain regional estimates. |
| Proportion of people living with hepatitis C who inject drugs | 22% | Based on country specific total PWID population size (Degenhardt et al.[37]) and prevalence among PWID (Nelson et al.[33]). Weighted averages used to obtain regional estimates. |
| Employment rate<br>*General population*<br>*PWID* | 53%<br>50% the employment rate of the general population | Country estimates from the World Bank[38]. Population-weighted averages used to obtain regional estimates.<br>Compared to a European average for paid employment (53% above), the proportion of PWID reporting regular employment ranged between 2-35% (Platt et al.[39]) |
| Proportion of people living with hepatitis C who have cirrhosis | 12% | Assumed |
| Treatment scale-up assumptions | | |
| Proportion of people cured who have cirrhosis | 24% | Assumed treatment uptake among cirrhotic patients is double non-cirrhotic patients. |
| Proportion of people cured who inject drugs | 22% | Assuming treatment uptake among PWID is equal to non-PWID. |
| Productivity loss parameters | | |
| Lost productivity attributable to hepatitis C<br>*Absenteeism*<br>*Presenteeism* | <br>1.03%<br>3.19% | <br>Dibonaventura et al.[40] US study. People with hepatitis C had 4.88% absenteeism versus 3.03% for people without hepatitis C.<br>Dibonaventura et al.[40] US study. People with hepatitis C had 16.69% presenteeism versus 13.50% for people without hepatitis C. |
| Additional productivity losses for people with cirrhosis<br>*Absenteeism* | <br>2.79 times | |

| | | |
|---|---|---|
| *Presenteeism* | 1.54 times | Younossi et al.[41] European study. Values are for compensated cirrhosis but also applied to patients with decompensated cirrhosis and hepatocellular carcinoma. |
| Relative reduction in absenteeism following hepatitis C cure | | |
| *Cirrhotic* | 44% | Younossi et al.[41] |
| *Non-cirrhotic* | 0% | |
| Percentage of hepatitis C-related deaths occurring at different age brackets | | |
| *15-29 years* | 0.2% | WHO cause-specific disease burden estimates, 2016[32] |
| *30-49 years* | 7.5% | |
| *50-59 years* | 16.4% | |
| *60+ years* | 75.8% | |

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## EASL Lancet Commission – pediatric disease management survey

Identification and model of pediatric liver care in Europe, focusing on biliary atresia and related diseases, support and transition.

Circulated as Survey Monkey using e-mail lists of EASL, ESPGHAN, EUPSA, ERN-rare liver and BARD-online.

**Information about the liver units**

**Country ;** _____

The setting of your unit is: (___) Part of an academic institution

(___) Tertiary care center

(___) Secondary care center

**Personnel**

Number of pediatric gastroenterologists/ hepatologists ____ (number)

Number of pediatric surgeons ____ (number)

Number of surgeons performing pediatric Liver-Tx ____ (number)

Specialist nurses (___) yes (___) no

Dieticians (___) yes (___) no

Psychologists (___) yes (___) no

Play therapists (___) yes (___) no

Family support organization (___) yes (___) no

**Diagnostic/therapeutic facilities**

Endoscopy: Therapeutic (___) yes (___) no

Magnetic resonance imaging (___) yes (___) no

Nuclear medicine (___) yes (___) no

ERCP (___) yes (___) no

Pathologist with experience in pediatric liver disease (___) yes (___) no

Metabolic Laboratory (___) yes (___) no

Genetics- next generation sequencing ( ) yes ( ) no

Others (___) yes (___) no

Please specify _____

_____

_____

Do you have an interdisciplinary established care pathway/ SOP for children with neonatal cholestasis at your center ? (___) yes (___) no (___) planned

**Member/partner of pediatric liver networks**

ERN rare liver (___) yes (___) no (___) planned

BARD-online (___) yes (___) no (___) planned

PFIC e.g. NAPPED consortium (___) yes (___) no (___) planned

Others, please specify _____

_____

_____

**Do you have screening programs for neonatal cholestasis/biliary atresia?**

National program (___) yes (___) no (___) planned

Regional program (___) yes (___) no (___) planned

Individual program (___) yes (___) no (___) planned

If "yes" or "planned", please specify _____

_____

**Do you know about and have access to patient and family support groups ?**

Local groups (based at your center) ( ) yes ( ) no

National groups (based in your country) ( ) yes ( ) no

Other groups ( based in other countries in Europe) ( ) yes ( ) no

**Are you taking part in patient registries?**

National registries (___) yes (___) no (___) planned

If "yes" or "planned", please specify _____

Individual (center) registry (___) yes (___) no (___) planned

If "yes" or "planned", please specify _____

ERN-rare liver registry (___) yes (___) no (___) planned

BARD-online (___) yes (___) no (___) planned

PFIC e.g. NAPPED (___) yes (___) no (___) planned

Others, please specify _____

_____

_____

**Transition program for pediatric liver diseases**

Do you have a transition program (___) yes (___) no (___) planned

Do you have a transition team? (___) yes (___) no (___) planned

Do you have a transition nurse? (___) yes (___) no (___) planned

Do you have a transition psychologist? (___) yes (___) no (___) planned

Do you have joint clinics with adult hepatologist? (___) yes (___) no (___) planned

Do you transition to agreed adult Unit? (___) yes (___) no (___) planned

**Caseload of pediatric liver diseases per center**

Please provide the number of new cases per year

Biliary atresia (___) new patients/year

Choledochal cyst (___) new patients/year

PFIC (___) new patients/year

Alagille (___) new patients/year

Autoimmune hepatitis (___) new patients/year