HEPAHEALTH II: a model to examine synergies between risk factors for liver disease and the impacts of potential interventions

On behalf of the EASL HEPAHEALTH Group:

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Summary

Liver disease mortality has changed dramatically over time, with four-fold increases and decrease in European countries in response to changing alcohol consumption. But the future burden of liver mortality will be dependent on complex synergies at a clinical and behavioural, level with further synergies between elements of health policy responses. New developments in big data and computing will enable us to create models of liver disease in representative European countries with high quality individual level data from surveys that can test the impact of various policies on hard outcomes: hospital admissions, mortality and health service costs. Thus enabling policymakers to develop evidence based policies to reduce liver mortality, hospital admissions and costs.

Aim

To create a health policy model for liver disease

Methods

Synergies between risk factors, behaviours and policies will be addressed using a modelling approach.

Expected Outcome

The model will facilitate the development of effective health policy by allowing policy makers and political actors to estimate the impact of various combinations of population level policy measures and specific clinical interventions on hard outcomes, namely: expected mortality, hospital admissions and costs.

The project will start as a feasibility study with modelling in no more than four European countries where we know the data systems are of sufficient quality to provide the required baseline data.

Introduction

Europe has the largest burden of liver disease in the world,(1) and this burden is expected to grow in many countries. Morbidity and mortality from liver disease vary between countries and within countries over time. For example, the UK and Finland have observed staggering increases in liver disease mortality over the last 40 years while the inverse is true for countries such as France and Italy, where liver disease mortality began declining in the 1970s and has continued to fall. These profound differences occur in part because of the prevalence of modifiable risk factors, such as harmful alcohol consumption, obesity, and viral hepatitis.

Worryingly, Europe has the highest per capita alcohol consumption and alcohol-related loss of disability adjusted life years of any of the global regions.(2)Obesity has increased markedly over the past four decades,(3, 4) and as a result, non-alcoholic fatty liver disease (NAFLD) is an increasingly prevalent liver disease in Europe.(2) Viral hepatitis as a risk factor for liver disease is less well documented.(2) Prevention of these risk factors and types of liver disease is important in order to

stop progression to other forms of liver disease such as liver cancer. Liver disease principally affects working age people; therefore, tackling risk factors will have impacts not just on the individual and health system, but on the economy.

Disease silos and synergies

Liver patients no longer fit neatly into disease silos. For example, hepatitis C results from viral infection – it is a typical infectious disease, and the rate of sustained virologic response with new directly acting antiviral is ≥95%. But alcohol synergises with the virus to increase liver fibrosis and the development of hepatocellular carcinoma(5), to the extent that in some countries 50% of cirrhosis in patients with HCV infection may be due to alcohol misuse(6). Similarly, alcohol and obesity are synergistic, to the extent that in patients with a BMI of more than 35, the hepatotoxicity of alcohol is doubled(7). In addition to these clinical synergies, there are behavioural synergies; patients with HCV have a two to four times increase in alcohol misuse(8). Alcohol consumption may contribute to obesity, and both risk factors are strongly linked to heath inequalities(9).

There is huge potential to reduce the mortality and morbidity of liver disease by tackling these risk factors at a population and individual level(10). In the first part of the Hepahealth project, we analysed the epidemiology of liver disease across the World Health Organization (WHO) European Region, and described the potential policy options to tackle the multifactorial risk factors that determine trends in mortality. In order to help formulate these interventions, the next step will be to model the complex interactions of risk factors that drive liver disease morbidity and mortality together with the interventions that we can use to reduce this burden.

Health policy modelling

On the whole politicians and policymakers do not subject policies to randomised controlled trials, due to their complexity. But increasingly governments and industry rely on modelling of policies to determine impacts, just as central banks and finance ministries rely on economic models to forecast the results of changes in interest rates and fiscal policy, for example.

The evidence base for these models consist firstly of studies that use hard data to establish and calibrate basic principles. An example would be the concept of elasticity; a fundamental economic metric which links the changes in the consumption of a product to changes in price(11). Similarly the principle that marketing impacts on the drinking behaviour of children has been proven in a series of longitudinal experimental studies(12). The size of this impact can be calculated, and elasticities determined for exposure to alcohol marketing(13).

These basic components can then be modelled to determine the impact of changes in price, or levels of marketing upon both consumption and the various aspects of harm, in the same way that a central bank will model the impact of changing interest rates on inflation. There are a number of models that have examined alcohol policy including: the WHO-CHOICE model(14-16), Australia's ACE- prevention programme(17), the Dutch chronic disease model(18), the EU Dynamo-HIA model(19, 20), the UK Sheffield model(21) and most recently the CDP-alcohol model developed by the OECD(22). The modelling findings are consistent, and were summarised by WHO as 'best buys'(23): tax increases on alcoholic beverages, comprehensive restrictions and bans on alcohol marketing and restrictions on the availability of retailed alcohol. Similarly, models have been developed which examine the impact of changing BMI at a population level on obesity related disease(3) and in viral hepatitis increasingly sophisticated modelling has raised the possibility of eliminating the disease from some environments(24-33).

The underlying mathematics of these models is complicated but essentially fall into two main categories. Initially models categorised individuals into groups, and then forecast behaviour according to the various elasticities to which are subjected(34). An example being the Sheffield Alcohol Policy Model used by the Scottish Government to develop a policy of Minimum Unit Pricing, and then defend and justify this policy through a series of legal challenges including at the European Court of Justice(35, 36).

Developments in information technology have resulted in more sophisticated dynamic micro-simulation models. These models consist of single virtual individual entities programmed to react in a changing environment. A single model may involve tens of millions of virtual actors, and as a result the models can be extremely flexible in simulating complex synergistic interactions. Micro-simulation models have been developed for smoking(37), alcohol(22) and obesity(3), but so far none of these models has been able to combine these various risk factors to help determine the impact of interventions in liver disease.

Aims of Hepahealth II

The explicit goal is to create a Micro Simulation Model for prediction of measureable liver outcomes, met by developing a model that combine results from randomized controlled trials, epidemiologic studies (e.g., case-control and cohort studies), meta-analyses, and expert options.

This model will address:

- Clinical synergies between alcohol consumption, obesity and the presence or absence of viral hepatitis (HBV and HCV) as a co-factor underlying the progression of liver disease to a stage where patients develop severe end stage liver disease or hepatocellular carcinoma, or die as a result of their liver disease.
- Behavioural synergies resulting in a clustering of risk factors and health inequalities;

McSM v other modelling approaches

McSM was highlighted as the best method for risk factor and chronic disease modelling by the OECD as referenced in their report 'Toward a New Comprehensive International Health and Health Care Policy Decision Support Tool' (Oderkirk et al, 2012).

Strengths include:

- allowing the testing of the potential impacts of policies and practices, through —what if scenarios and the related costs of implementation e.g. what is the expected impact on CVD incidence following the implementation of a tobacco escalator tax
- time, cost and ethical advantages of using simulation models vs experiments, which are not possible with population level policy interventions
- enabling a wide set of comparisons to identify the most promising combinations of prevention (including policy interventions), screening and treatment approaches for different types of patients (as in the UKHF EConDA project econdaproject.eu)
- going beyond the follow-up periods of typical clinical trials so that long-term outcomes can be compared 20, 30, 50 years into the future
- going beyond narrow definitions of study outcomes to outcomes in real-world settings where patients are complex and remain at risk of developing a wide range of disease conditions (i.e. accounting for comorbidities)

- help inform and persuade decision makers to make the best decisions possible

Importantly, dynamic microsimulation is the only modelling approach that is applicable if an individual‘s history matters. For example, an individual‘s history of risk-taking behaviour, such as smoking, alcohol use and nutrition matters for the development of certain diseases, and this is certainly the case for liver disease. An individual‘s history of disease matters for whether they live or die. Microsimulation models are designed to remember an individual‘s history and take it into account to influence their future life course.

Some of the strengths of the McSM could potentially be achieved through dynamic compartmental modelling with appropriate stratification; there are examples of compartmental models which incorporate complex interactions between risk factors and diseases. Although compartmental models don’t have memory per se, but this can, up to a point, be achieved through stratifying the population into groups which have different history of risk taking and comorbidities. We will therefore be prepared to look at tenders which employ compartmental modelling, proving the justification shows how our objectives can be achieved with this approach.

Specification of Hepahealth Model (38)

We envisage a model which will be able to estimate the effect of different clinical interactions and health policies on hard outcomes: hospital admissions, mortality and economic costs in different European member states.

In the first instance, the modelling will examine alcohol and obesity, determining how changes in individual level consumption of various alcoholic beverages and dietary intake of obesogenic food and drinks, interact to cause progression to advanced chronic liver disease, hepatocellular carcinoma and / or mortality.

We envisage the modelling will be performed initially in no more than four sample European countries with different trajectories of liver disease, in Western, Central and Southern Europe, with further funding sought for individual countries to expand the model over time.

Modelling of viral hepatitis is currently much further advanced than obesity or alcohol. We envisage a further stage of Hepahealth II, whereby we will seek to expand the obesity / alcohol model to include viral hepatitis, most probably in collaboration with one of the centres of viral hepatitis modelling expertise.

The model will have two components: a natural history model and an intervention model. The natural history model will describe the disease process in the absence of intervention, and be combined with the interventions model to answer policy questions.

The three essential objectives in developing the model will be:

1) Identifying a fixed number of distinct states and characteristics associated with these states;
2) Specifying stochastic rules for transition through states;
3) Setting values for model parameters.

This combining of information will be an implicit modelling goal and conducted in conjunction with model calibration. The function of the model will be to simulate a hypothetical population with specific characteristics, such as a specific age-sex distribution, and specific risk factor profiles.

Potential parameters include:

- Population / environmental - demographics, deprivation, wealth, ethnicity, price, affordability, levels of taxation and other economic indicators, cultural indicators
- Alcohol – consumption of alcohol subtypes, drinking days, drinks / day.
- Obesity – body mass index (BMI), type 2 diabetes / metabolic syndrome
- Viral hepatitis (HBV and HCV) – status
- Interventions – individual clinical interventions, fiscal including MUP, marketing restriction, availability restrictions.

Deterministic or probabilistic sensitivity or uncertainty analyses will be required with multivariate variate analyses as parameters tend to interact nonlinearly.

We encourage modellers to focus on both parametric and structural uncertainties. For example, structural uncertainties could relate to the number of discrete health states in your model, the inclusion of comorbidities, the rules governing the transitions between the states, and so on.

Hard outcome metrics should include mortality with years of working life lost, hospital admissions and QALYs

The model will be calibrated using historical data and assessment of the calibrated model will include validation, examination of sensitivity to untestable assumptions, and incorporation of variability. We envisage for each of the country models we have data for, data will be partitioned into independent sets so that a proportion of the data is kept for validation whereas the rest is used for parameterization. Transparency will be required with disclosure of the model's assumptions (including relative costs) and algorithms.

Process

We envisage that following approval from the EASL Governing Board, the next step will be an open call for brief expressions of interest from specific modelling groups. Potential tenders will include an outline (1500 words) of methodology, outcomes, countries to be modelled, and costs, deadline 31 October 2018.
The EASL Board will approve the project subject to funding at its December 2018 meeting. This process will inform both the research groups and EASL, and will provide a specific knowledge base on which to seek external funding.
Once funding has been obtained further more detailed bids will be sought from the shortlisted organisations (a call for tender to be launched in December 2018, deadline 31 January 2019, selection and approval of final bid at the March EASL GB, start of the project, April 2019, all deadlines tbc subject to funding).

Funding:

EASL is investigating funding opportunities for this work. Work is planned to start in April 2019 and end no later than December 2020.

Dissemination: It is anticipated that the work carried out in HEPAHEALTH2 will:

- Be published as a report for launch at the ILC 2021
- Be submitted in article form for publication in a peer-reviewed journal (the Journal of Hepatology or another) and provide content for a dedicated symposium at ILC 2021.

- Strengthen and inform EASL's policy and advocacy work at EU and member state level, particular on alcohol and food policy, as well as viral hepatitis and HCC
- Provide background support and context for work to be carried out in a project on liver bioengineering which is currently the subject of an application to H2020 (tbc October 2018)
- Support the work of the EASL Lancet Liver Commission for Europe (April 2018-April 2020)

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