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The principles of policies to reduce the burden of liver disease

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Abstract

The dose-response relationship between alcohol and alcohol-related liver disease is exponential, as a result and in contrast to many other alcohol related harms, the majority of liver mortality occurs in heavy daily drinkers who seek out cheap strong alcohol. Price elasticities for very heavy drinkers are difficult to determine as this group are not represented in population studies. Nonetheless, data from the UK shows a strong relationship between the affordability of alcohol and liver mortality clearly demonstrating that these heavy drinkers are in fact extremely price sensitive. Interventions targeted towards very heavy drinkers, such as a minimum unit price for alcohol, are highly effective and cost-effective policies that can reduce liver mortality with practically no impact on low-risk drinkers.

Key Words

Alcohol; Alcohol-related liver disease; Policy; Intervention: Minimum Unit Price

Introduction

The liver is the largest organ in the body, the most metabolically complex, and probably the least well understood by non-liver doctors, as well as the general public. You can find the functional equivalent of the heart, lungs, and kidneys in a cheap aquarium. Simple mechanical devices can support life when these organs fail, but the same is not so for the liver which makes the building blocks of the body and detoxifies all the waste products. Prometheus was bound to a rock and visited every day by an eagle who eats half of his liver which then grew back overnight, only for the cycle to be repeated. The liver does indeed have remarkable powers of recovery. Following a single acute insult, the liver will usually regenerate. If a competent hepatobiliary surgeon removes half of the liver, then it can be expected to grow back within weeks to its full previous size and function. However, the response to repeated insults is quite different. Hepatic stellate cells are activated to secrete collagens and fibrosis, or scarring, develops as a wound healing mechanism. Nodules of liver cells surrounded by scar tissue look like a bag of marbles and regeneration is constrained. At this stage, the liver has developed cirrhosis – first described by Hippocrates in the fifth century BC. The other important disease process to affect the liver is carcinogenesis. Following repeated rounds of regeneration mutations develop with liver cells, and eventually primary liver cancer is the result.

Liver cirrhosis resulted in 223,000 deaths in the World Health Organization (WHO) European region in 2019, with a further 63,000 deaths from primary liver cancer, in total.[1] The majority of these deaths resulted from alcohol consumption (probably between 60% and 80%), but it is not possible to be exact because the coding of liver disease is poor in many European countries and aetiology is very often not recorded.[2] Liver disease causes 3% of deaths in Europe, but unlike the other major killers of the 21st century – the diseases related to smoking and obesity – liver disease kills people of working age. In terms of years of life lost in working age, liver disease is the second leading cause after ischaemic heart disease, killing more younger people than lung cancer, breast cancer, or diabetes (Figure 1).[1]

Over the last few decades, European countries have experienced differing trends in liver mortality rates. In Figure 2, we have categorised a selection of larger European nations into five groups according to their trajectory of liver mortality between 1990 and 2019 using the latest Global Burden of Disease (GBD) modelled data.[3] A small group of Eastern European countries have always had very high levels of liver mortality comprising in this selection: Moldova, Hungary and Romania. A group comprising: Sweden, Norway, Greece, Ireland, the Netherlands, and Malta have had stable low levels of liver mortality. Moldova has a standardised death rate (SDR) from cirrhosis and chronic liver disease of 74 per 100,000

population which is 10-fold higher than the rate seen in Norway which is 7 per 100,000 population. There have been changes in liver mortality over the past three decades. France, Spain, Italy, and Portugal have seen marked decreases in the rate of liver deaths as a result of substantial decreases in the consumption of cheap wine.[4] Whereas in the group comprising: Ukraine, Bulgaria, Belarus, Poland, Latvia, Estonia, Finland, and the United Kingdom, liver mortality has risen. These data clearly demonstrate that there is nothing fixed or irrevocable about dying from liver disease. There are factors within countries that determine the 40-50-fold differences in liver mortality, and the fact that liver mortality can increase or decrease 4-5-fold over a few decades demonstrates that these factors do change and can be changed. By understanding and changing these key drivers, we could dramatically reduce liver mortality in Europe (Figure 2).

The situation for liver patients in Europe is grim, but it need not be. There are simple cheap solutions that could be implemented given a desire to improve the health of people in Europe and a degree of political will. The evidence for these solutions is well established and can be described in terms of some simple principles and relationships.[5] In this chapter we will examine the nature of these relationships.

Implications of the exponential relationship between alcohol consumption and liver disease

Alcohol is a dose dependent toxin and there is a lethal dose of alcohol for anyone, however liver toxicity results in progressive liver fibrosis over 10-30 years followed by episodes of acute on chronic liver failure or variceal bleeding from portal hypertension. Liver mortality is usually related to these episodes which are strongly related to recent drinking, if alcohol consumption stops, the prognosis improves immediately. Liver disease is just one facet of health harm from alcohol and comprises around 25% of the attributable mortality with hypertension, stroke, cancer and mental and behavioural problems comprising the remainder.[6]

There are over 200 International Classification of Disease (ICD-10) codes with alcohol in their name. Some conditions are partially caused by alcohol, such as cancer, and others are entirely caused by alcohol, such as alcohol-related liver disease. For cancer, the dose response relationship is linear – the relative risk (RR) increases at levels above zero intake to 2.41 (95% confidence interval [CI]=2.07, 2.80) at an intake of 100g / day (Figure 3).[7] Large numbers of people are at a relatively low risk of alcohol induced cancer, but this adds up to a lot of people developing alcohol-related cancer, with an estimate of around 80,000 deaths and 1.9 million years of life lost in Europe in 2016.[8] Because of the linear risk between alcohol and cancer, the majority of cancer cases occur in moderate drinkers, and heavy drinkers account for a minority of the overall burden. In contrast, the dose response relationship for cirrhosis is

exponential, although heterogeneous with RR between 10 and 70 at 150g / day.[9] As a result of this relationship, the burden of liver disease is concentrated among the relatively smaller group of heavy daily drinkers with a high alcohol intake.

If alcohol-related liver disease is dose-dependent at the individual-level, then it follows that it must also be dose-dependent at the population-level. A seminal paper by Milton Terris in 1967 illustrated the very close relationship between mortality from liver cirrhosis and population-level consumption of strong alcohol (wines and spirits) concluding: "The evidence strongly supports the conclusion that cirrhosis mortality is directly related to per capita consumption of alcohol from spirits and wine" (Figure 4).[10] The concept developed by Kettil Bruun and Griffith Edwards forms the basis of modern alcohol control policy. Ceteris paribus – all else being equal – the proportion of heavy and extreme drinkers remains similar. This 'population consumption theory' forms the basis of modern alcohol control policy,[11-13] as the late Professor Griffith Edwards stated: "the overall level of a population's drinking is significantly related to the level of alcohol-related problems which that population will experience".[11] This means that the most effective interventions to reduce harm are those that target the whole population. This assumption generally holds for conditions with linear dose-response curves, such as cancer, where the majority of health harm is found among the larger number of moderate drinkers. However, the dose-response curve for alcohol-related liver disease is exponential (Figure 3), and as a result, cases are concentrated among a small group of heavy and extreme drinkers. Interventions targeted towards these heavy and extreme drinkers are likely to have a disproportionate benefit in terms of reducing liver mortality.

The "unit of alcohol" or "standard drink"

In academic studies alcohol is generally quantified in g/day, but alcohol is a liquid, alcoholic beverages are liquids and are sold in liquid measures. Furthermore the %ABV of alcohol is equivalent to the number of centilitres (cl) of pure alcohol in one litre of product. With this information it becomes very easy to calculate the number of cl of pure alcohol in any drink.

In communicating health risks to the public health agencies tend to talk about units of alcohol or standard drinks but there is no such thing. Wikipedia lists the various "standard drinks" in Europe, they vary from 8g in UK, 10g in France, 12g in Finland, 17g in Hungary and 20g in Austria.[14] This is utterly nonsensical, a sensible system would have a single standard measure of alcohol for public facing and academic facing communications, and the sensible choice would be to use one centilitre of alcohol as this standard measure. Many years ago we made this proposal to the European Health and Alcohol Forum, and over the life of the forum this was the single only proposal enthusiastically supported by both health and industry delegates.

Establishing an EU standard alcohol measure at one centilitre is extremely low hanging fruit for a public health measure and should be prioritised

It's hard to get cirrhosis - liver disease kills extreme drinkers

Alcohol-related liver disease is attributed to a single cause – heavy daily or near daily consumption – and the burden is concentrated among heavy and extreme drinkers. These drinkers are underrepresented across almost all routine datasets, but purposively sampled observational studies shed light on their typical consumption.

A pooled analysis of almost 3,000 patients across seven countries demonstrates the very large volumes of alcohol consumed by patients with alcohol-related liver disease.[15] Almost half of the sample (45%) reported drinking >110g of alcohol / day (96cl / week), more than three bottles of vodka each week. A further 44% reported drinking between 80-160g of alcohol / day (70-140 cl / week). The average daily consumption reported across the studies ranged from 65g to 176g / day (56 – 154 cl / week). Drinking an average of 84g / day (73cl / week) increases the risk of liver cirrhosis almost seven times in men (RR=6.93, 95% CI=1.07, 44.99) and over 12 times for women (RR=12.44, 95% CI=6.65, 23.27).[16]

In a British study the mean weekly consumption reported by patients with alcohol-related liver disease presenting to a large hospital was around 150cl / week (Figure 5).[17] In a second sample of patients with alcohol-related cirrhosis or progressive fibrosis, the median weekly consumption was almost 75cl / week.[18] Across a decade of household surveys in England, less than 1% of respondents reported drinking at equivalent levels to those reported in liver patients

Only a minority of patients with alcohol-related liver disease have evidence of severe alcohol dependency,[18-20] however daily drinkers with alcohol dependency have an eightfold increase in the incidence of cirrhosis.[21] In drinkers presenting to services with serious alcohol problems in Scotland, the median reported weekly consumption was almost 1,500g / week.[22] Among Scottish females drinkers presenting to these services the median was around 1,200g / week.[23] Similarly high volumes were reported in a cohort of patients undergoing medical detoxification in New Zealand at 1680g / week.[24]

The dose response relationship for alcohol-related liver disease means that heavy and extreme drinkers are at exponentially higher risk and decreases in consumption will reduce the risk of death per drink substantially more than the risk reduction experienced by lower risk drinkers.

Extreme drinkers buy cheap booze

As demonstrated in the previous section, people with alcohol-related liver disease report extremely high volumes of alcohol consumption – around 3.5 bottles of vodka per week.[15] As a result, they seek out cheaper alcohol. These extreme drinkers are underrepresented in general household surveys or consumer panels, so the limited data available to demonstrate this principle comes from observational studies specifically sampling heavy drinkers.

In England, patients with alcohol-related liver disease reported paying less than one-third of the price paid by lower risk drinkers per 10cl of alcohol.[17] Lower risk drinkers spent an average of almost £500 on alcohol each year, which is the amount spent by higher risk drinkers in less than two months. In Scotland, patients with serious alcohol problems reported paying, on average, 1.7 times less per 10cl of alcohol compared to the average price paid by drinkers in the general population.[25] When the sample was limited to those drinking at least 1,600g / week, the amount paid per 10cl of alcohol was almost 2.5 times less than that paid by the general population.

Price elasticity of extreme drinkers

The consumption of alcohol is to some extent determined by price or affordability. This relationship is described as an elasticity, which is the percentage change in consumption resulting from a 1% change in price. The recent systematic review by the Organisation for Economic Co-Operation and Development found that beer is the least price-sensitive beverage (with elasticities ranging from -0.29 to -0.83) compared to wine (-0.46 to -1.11) and spirits (-0.54 to -1.09), and that moderate consumers were slightly more price sensitive compared to heavier consumers with an additional elasticity of around 0.05% (heavier consumers were defined as ≥40g / week and ≥20g / week for men and women respectively).[26] Heavier drinkers consumed around twice as much alcohol below a specific price threshold compared with moderate drinkers showing their clear preference for cheap alcohol.[26]

However, the price elasticity of the very heavy daily drinkers who comprise the majority of patients with alcohol-related liver disease has never been specifically determined because they are not represented in population studies. Studies in clinical populations have confirmed patients with alcohol related cirrhosis or alcohol dependence have a clear preference for cheap strong alcohol,[17,25] and confirm that certain types of very cheap strong alcohol such as ‘white cider’ in the UK are consumed almost exclusively by very heavy drinkers.[27]

In the UK, liver mortality rates have increased almost three-fold since 1980 and the relationship between trends in mortality and the underlying changes in alcohol affordability are clear to see (Figure 6).

Using duty receipt data from Her Majesty's Revenue and Customs and death data for England and Wales from the Office for National Statistics, the elasticity between total alcohol consumption and alcohol affordability was 0.41%, exactly what would be expected from the various meta-analyses (Figure 7).[28,29] However, it is also possible to examine the direct relationship between alcohol affordability and mortality rates from alcohol-related liver disease, and calculate a direct elasticity, which in this case is 3.2% – six times higher than the elasticity on consumption (Figure 8). This is similar to an estimate published in two systematic reviews which reported the elasticity for cirrhosis mortality to be around 3.5% (for reference, the elasticity for suicide was 0.5%).[30,31]

Alcohol-related and liver mortality are strongly linked to health inequalities.[32,33] The most likely explanation for this dramatic increase in elasticity is that extreme drinkers who die from alcohol-related liver disease are extremely price sensitive because they have already maxed out their spending on cheap alcohol. A price increase can be a stimulus to change behaviour, and in the case of extreme drinkers this will often be to stop drinking all together, thus reducing immediately their projected likelihood of death.[34]

Models of policy interventions

About 80% of deaths directly caused by alcohol are from alcohol-related liver disease, and around a further 10% are from alcohol dependency,[635] so the drinking behaviour of these two groups are absolutely critical to the accurate modelling of minimum unit price (MUP).

The Sheffield model uses survey data to estimate the impact of MUP, and because heavy and extreme drinkers are substantially underestimated in these surveys, the result is a model which underestimates the policy's impact on alcohol-related liver mortality. The model reports the mean alcohol intake among harmful drinkers to be 571.2g / week,[36] which is 878.8g less than the 1,450g / week reported in a sample of patients with alcohol-related liver disease.[17] Considering the incidence of alcohol-related liver disease in heavy drinking cohorts is between 10-20 times greater than the incidence seen in the general population,[37,38] the impact of this underestimate is likely to be substantial. The model estimates the yearly spend by higher risk drinkers to be £2,862, which is £570 less than the average yearly spend on alcohol reported by the patient sample (£3,432).

Minimum Unit Price in Scotland

The epidemiological, clinical and alcohol control policy evidence described previously presents a compelling case for action to prevent alcohol-related harm. Yet for many countries while levels of harm remain unacceptably high the implementation of the most impactful control policies has not materialised.[39] While the scientific evidence defines the nature and

scale of a problem it is Government and politics that plays the central role in implementing effective control policies.

Health advocacy can play a key role in influencing policy change. This is more likely to be impactful if done from an informed position of the nature of policy making and which policy makers to target. Advocates will need to consider how best use to use their limited resources, their knowledge and experience to communicate the problem and solutions to policy makers and the public.

The policy making process is rarely a stable and linear process.[40] The reality is a more dynamic irrational process constructed through engagement with multiple actors often holding conflicting views on a given topic. This can be challenging for health professions and advocates to navigate as often they are used to a rational evidence-based approach. While scientific evidence derived from structured methods and subject to peer review, policy making is a "loosely organised body of precepts and positions".[41]

Policies that are aimed at preventing or reducing harm from commercial products such as alcohol that can damage health can be challenging to influence due to favoured political view on individual responsibility borne out of prevailing neoliberalism and the influence of lobbying of commercial actors.[42] Health advocates can play a key role in countering these views putting forward strategies based on equality and evidence.[43]

While no framework of policy making fully captures the complexity of its reality, Kingdon's 'multiple streams approach' presents a dynamic model which can aid understanding of how some issues are addressed through policy changes and others are not.[44] It identifies three relatively independent streams or processes that when they converge create a window of opportunity through which policy change is more likely to occur (Figure 9).

Advocates can influence each of the three streams and play an important role facilitating the convergence of the streams. This facilitation needs leaders, often outside of Government who can bring about policy change through the matching of problems, policy options and political support.[45] Success depends on gaining support from those in key political positions who can bring about change. Focusing on the following three areas can increase the likelihood of success:

- Making the case on the necessity to act
- Identifying the decision-making venues and procedures to pursue the proposals
- Adapting proposals to generate support and overcome opposition

How policy making works – does evidence matter?

Over recent decades, medical organisations and advocacy groups across the UK and Ireland have been vocal in their concern about health harm from alcohol. They have highlighted the burden and causes of harm, evidence-based solutions, and campaigned for Governments to do more.[46-48]

Epidemiological data has been influential by identifying the burden of harm and the adverse trends. A 2006 study comparing the mortality rates from liver cirrhosis across the UK[49] has been identified as being influential in starting to change the narrative on Scotland's relationship with alcohol.[50] The study presented stark data showing mortality rates in Scotland were one of the highest in Western Europe, and had been rapidly increasing since the 1990's.[49]

Evidence and expert opinion played an important role in identifying solutions to preventing and reducing alcohol-related harm including novel approaches to address the affordability of alcohol. In 2007, the advocacy group Scottish Health Action on Alcohol Problems published a report that linked alcohol's affordability with harm.[48] A key recommendation for the Scottish Government was to establish minimum prices for alcoholic drinks. A year later, a econometric study identified MUP as an effective measure to target those most at risk of harm.[51]

Kingdon's policy theory suggests that problem recognition and solutions need to converge with political will to create the conditions conducive to policy change. The establishment of the Scottish Parliament in 1999 with responsibility health policy and the election of the Scottish National Party in 2007 opened up political consideration to wider prevention policies including addressing public concern about the availability and affordability of alcohol.[52] This paved the way for the Scottish Government to pursue MUP which came into force in May 2018. Ireland and Wales have now also implemented MUP, and Northern Ireland has consulted on implementation.

All fiscal policy, whether tax or MUP, is targeted because the impact is directly proportional to the amount alcohol consumed. While tax affects all drinkers, MUP is highly targeted, affecting those cheap high strength products favoured by heavier drinkers, and as such has the greatest potential to reduce health inequality.[53] Tax and MUP are therefore complimentary policies.[54] This has been confirmed by the highest courts in Europe and UK after a challenge by the alcohol industry that it have a detrimental impact on trade. The UK supreme court unanimously concluded that MUP in Scotland is *"a proportionate means of achieving a legitimate aim"* and in terms of the impact on health vs trade impact *"That minimum pricing will involve a market distortion, including of EU trade and competition, is accepted. However, I find it impossible, even if it is appropriate to undertake the exercise at all in this context, to conclude that this can or should be regarded as outweighing the health benefits which are intended by minimum pricing"*.[55]

While most producers have been against the policy, several retail bodies been in favour including supermarkets.[56] The extra income generated by MUP goes to retailers so therefore isn't a tax.

The media has a powerful role in agenda-setting and influencing public opinion this in turn can influence policymaker's and shape a government's response. Inaction by politicians to address an issue may in part be influenced by concerns relating to media backlash from legislative changes. An unpublished study suggests these concerns are unfounded and since the implementation of MUP in Scotland the majority of media discourse has been supportive of MUP (Robyn Burton unpublished data). Studies of media and political impact showed no adverse political impact (ibid). The fact that MUP is a highly targeted measure that does not affect the low-risk consumers that do not purchase the cheapest strong alcohol was central to the court judgements and hugely important to the favourable public and media response to MUP. Perhaps it is time for the alcohol policy community to re-evaluate their aversion to targeted alcohol policy measures.

The divergence of policy in relation to MUP across the UK nations and Ireland has created a controlled natural experiment with England as the no treatment control. This will produce important evidence on the impact of MUP on health harm and identify any unintended consequences.

Conclusions

Alcohol-related liver disease is a substantial public health burden but need not be. There are factors between countries that determine 40-50-fold differences in liver mortality across Europe.[3] Liver mortality within countries can increase or decrease 4-5-fold over a few decades demonstrating that these factors change and can be changed. There are simple cheap solutions that could be implemented given a desire to improve the health of people in Europe and a degree of political will. The underlying principles are straightforward. The dose-response relationship between alcohol and liver fibrosis is exponential, as a result, the majority of liver mortality occurs in heavy daily drinkers who seek out cheap strong alcohol. This group are not represented in population studies and price elasticities for alcohol consumption are undetermined. However, data from the UK shows a strong relationship between the affordability of alcohol and liver mortality clearly demonstrating that these heavy drinkers are in fact extremely price sensitive. Interventions targeted towards very heavy drinkers, such as a minimum unit price for alcohol, are highly effective and cost-effective policies that can reduce liver mortality with practically no impact on low-risk drinkers. The solutions for alcohol related liver disease, the largest cause of liver death in Europe by a country mile, do not lie in expensive hepatology units or with Big Pharma. The solution is simply to set realistic minimum

prices per centilitre of pure alcohol across Europe. As the results of the ongoing controlled natural experiments in alcohol policy become clear the political imperatives to do this will become overwhelming.

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