Review

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Treating alcohol-related liver disease from a public health perspective

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Summary

Herein, we describe the evolving landscape of alcohol-related liver disease (ALD) including the current global burden of disease and cost to working-aged people in terms of death and disability, in addition to the larger spectrum of alcohol-related heath complications and its wider impact on society. We further review the most effective and cost-effective public health policies at both a population and individual level. Currently, abstinence is the only effective treatment for ALD, and yet because the majority of ALD remains undetected in the community abstinence is initiated too late to prevent premature death in the majority of cases. We therefore hope that this review will help inform clinicians of the "public health treatment options" for ALD to encourage engagement with policy makers and promote community-based hepatology as a speciality, expanding our patient cohort to allow early detection, and thereby a reduction in the enormous morbidity and mortality associated with this disease.

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Introduction

Alcohol is a leading commodity, along with tobacco and foods high in salt and sugar, responsible for the rise of non-communicable diseases, which now account for over 70% of deaths globally.[1] It remains the only psychoactive substance with a global impact on health that is not controlled by international regulatory frameworks, such as the Framework Convention on Tobacco Control.[2] While social drinking has long been acceptable, we now know that all levels of consumption are associated with some degree of harm and there is robust evidence that low levels of intake do not provide any protective health benefits.[3] Including liver disease, alcohol has been linked to 23 health-related outcomes.[3] Alcohol dependence can lead to cirrhosis and liver cancer both of which are often detected too late to prevent premature death in nearly 75% of cases.[4] Furthermore alcohol abuse is associated with massive losses in productivity, damage to families and communities, violence and injuries. Liver disease stands apart from other chronic diseases as it affects young and middle-aged individuals. Significantly, alcohol was the leading cause of death among 15–49 year olds globally in 2016, associated with 12.2% of male and 3.8% of female deaths.[3]

Both models and natural examples have identified that the most effective policies for reducing alcohol-related harm include price increases on alcoholic beverages (particularly minimum unit pricing), bans on alcohol marketing and restrictions on the availability of retailed alcohol.[5–7] The striking benefit of population level interventions is that they have been shown to affect alcohol-related mortality within 2 years, because reduced consumption can lead to rapid improvements in mortality, including in individuals with established cirrhosis.[8,9] Leadership at a national level continues to be lacking. However, as politicians choose voluntary commitments and a hand-in-hand relationship with industry over evidence-based policies in the majority of countries, the statistics for alcohol-related harm in these states continue to make headlines.

The burden of alcohol-related liver disease and links to environmental factors

The Global Burden of Disease project estimated over 1.25 million deaths occurred due to liver disease in 2016 (2.3% of the global average).[10,11] This represents a significant increase since 1980 (676,000 deaths, 1.5% global average).[12] The prognosis for patients with alcohol-induced cirrhosis is extremely poor, with mortality rates of 71% at 5 years and 91% at 15 years.[13] The largest consumers of alcohol worldwide, in which more than half of the population drink some alcohol, are in Europe (particularly Eastern Europe and Russia), followed by Australia and Northern America.[2,14] Just over a third of deaths from liver disease are reported as alcohol-related in these countries.[12] However, the burden is likely to be considerably higher due to a large proportion of liver-related deaths being coded with an unknown aetiology (Fig. 1). In reality it is estimated that around 60–80% of deaths from liver disease are due to alcohol excess in high-income countries.[15]

Of huge importance is the that fact two-thirds of all potential years of life lost from liver disease-related deaths are working years.[16] This strongly contrasts with other major chronic diseases, for example ischaemic heart disease, stroke and lung cancer where the proportion is approximately one-third.[16] In 2015 more than one million years of life were lost in Europe before the age of 50 due to cirrhosis, with at least a third being alcohol-related.[17]

Key points

The estimated burden of liver disease has increased over the last 4 decades, with liver disease accounting for 2.3% of deaths in 2016 compared to 1.5% in 1980.

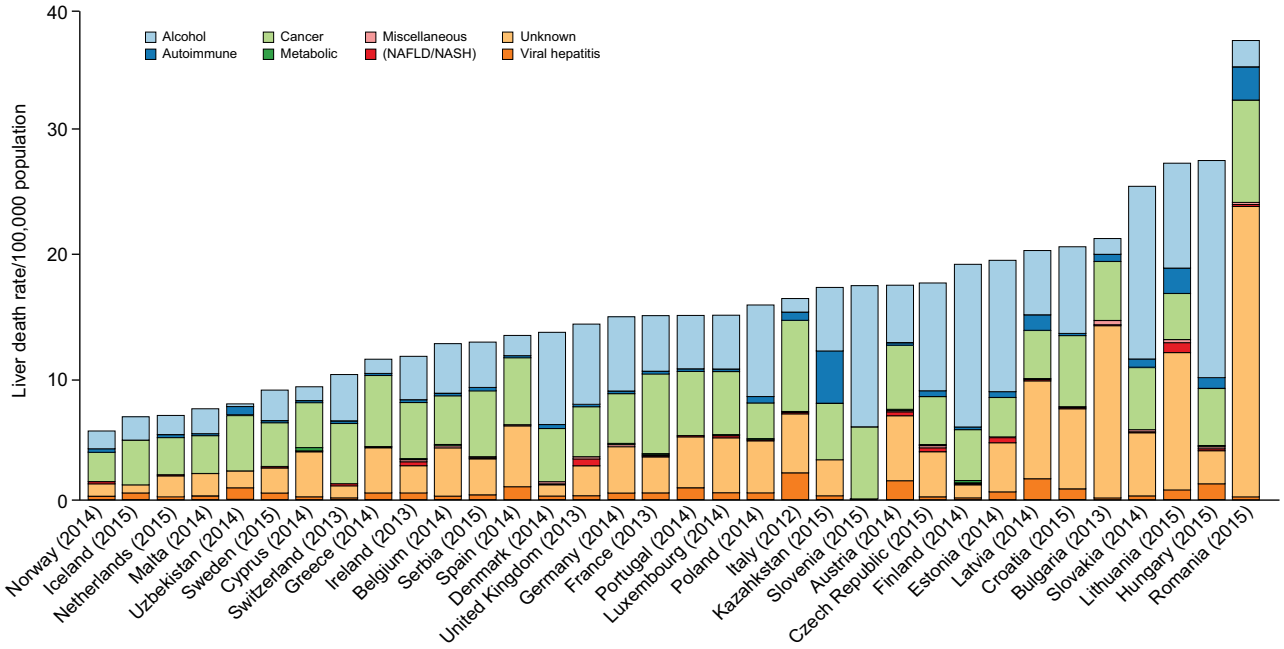

Fig. 1. Age-standardised mortality rate from all liver diseases by type (in the most recent year available for each European country). Data sourced from WHO Detailed Mortality Database.[171] Adapted with permission from the HEPAHEALTH project report.[16] NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; WHO, World Health Organization. Alcohol: K70 Alcohol-related liver disease. Autoimmune: K73 Chronic hepatitis, not elsewhere classified, K74.3 Primary biliary cirrhosis, K74.5 Biliary cirrhosis, unspecified, K75.3 Granulomatous hepatitis, not elsewhere classified, K75.4 Autoimmune hepatitis, E83.0 Disorders of copper metabolism. Cancer: C22 Malignant neoplasm of liver and intrahepatic bile ducts. Metabolic: E83.1 Disorders of iron metabolism, K75.8 Other specified inflammatory liver diseases. Miscellaneous: K74.4 Secondary biliary cirrhosis, K75.0 Abscess of liver, K75.1 Phlebitis of portal vein, K75.2 Nonspecific reactive hepatitis, K76.1 Chronic passive congestion of liver, K76.2 Central haemorrhagic necrosis of liver, K76.3 Infarction of liver, K76.4 Peliosis hepatitis, K76.5 Hepatic veno-occlusive disease, K76.8 Other specified diseases of liver, K77 Liver disorders in diseases classified elsewhere, K72.0 Acute and subacute hepatic failure, K72.1 Chronic hepatic failure, K72.9 Hepatic failure, unspecified. NAFLD/NASH (Fatty): K76.0 Fatty (change of) liver, not elsewhere classified, K71 Toxic liver disease. Unknown: K74.6 Other and unspecified cirrhosis of liver, K76.6 Portal hypertension, K76.7 Hepatorenal syndrome, K74.0 Hepatic fibrosis, K74.1 Hepatic sclerosis, K74.2 Hepatic fibrosis with hepatic sclerosis, K75.9 Inflammatory liver disease, unspecified, K76.9 Liver disease, unspecified, I85 Oesophageal varices, I81 Portal vein thrombosis, I82.0 Budd-Chiari syndrome, I98.2 Oesophageal varices without bleeding in diseases classified elsewhere, I98.3 Oesophageal varices with bleeding in diseases classified elsewhere. Viral hepatitis: B15-B19 Viral hepatitis.

Global trends in liver disease over time

From 1980 to 2010, age-standardised mortality rates from liver cirrhosis decreased in North America, Australia, Southern and Western Europe, East Asia, North Africa and the Middle East, but increased in South and Central Asia, Eastern Europe, Finland and the United Kingdom (UK), where population attributable fractions of ALD have increased over these 3 decades.[12] These trends are likely to continue as according to the World Health Organization (WHO) 2018 global status report on alcohol and health, per capita levels of alcohol consumption have decreased from 2005 to 2016 in the majority of European countries from 12.3 to 9.8 litres per annum (although this WHO region remains the largest consumer of alcohol per capita), but has risen in WHO Western Pacific and South-East Asia regions, where it is predicted to grow until 2025, as is consumption in North and South America.[2] Alcohol consumption has increased in China faster over the last 30 years than anywhere else in the world, because of economic growth, although a significant proportion of production remains unrecorded.[18,19] Indeed this remains the case for one-quarter of all alcohol consumed worldwide.[2] The United States (US) is also currently experiencing an alarming rise in harmful drinking. The National Epidemiologic Survey on Alcohol and Related Conditions reported nearly a 50% increase in the prevalence of alcohol use disorders between 2001–2002 and 2012–2013.[20] Increases were particularly high for women, older adults, ethnic minorities and socioeconomically disadvantaged individuals.[20] The National Survey on Drug Use and Health estimated that 88,000 alcohol-related deaths occurred in 2015, making alcohol the third most frequent cause of preventable death in the US.[21] An increase in the prevalence of alcoholic hepatitis has been reported over a similar time period.[22] The rise in harmful drinking may in some part be driven by the current "opiate crisis",[23] as individuals suffering from addiction are likely to abuse multiple substances. The "opiate crisis" has largely overshadowed the "alcohol addiction crisis" in the media, despite the abuse of opiates and other illegal substances being less prevalent overall.

Within Europe there is a huge heterogeneity between countries in terms of liver deaths, with decreasing mortality rates in Western and Southern Europe since 1970, and high stable or increas-

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ing levels across Northern and Eastern European countries (Fig. 2). These trends are largely mirrored by population level alcohol consumption.[15] Changes in drinking patterns can also influence death rates from liver disease. In the UK increases in liver mortality were associated with only modest increases in overall consumption, but were linked to a switch from weak beer consumed in pubs, to stronger alcohol (wine, spirits, strong cider) bought cheaply and drunk at home, which is associated with a binge-drinking culture (Fig. 3).[24–26] Similarly heavy episodic drinking remains extremely high in parts of Eastern Europe.[2] In contrast, France and Italy have experienced a year-on-year reduction in overall alcohol consumption driven by reduced consumption of cheap wine, with consumers choosing quality over quantity.[15] These changes were mirrored by a 4-fold reduction in liver deaths, moving these countries from the top 30th centile globally for liver mortality to the lowest 30th percentile within 20 years.[15] Furthermore spirit consumption has decreased by 3% in Europe overall since 2010, the most significant switch in consumption worldwide over this period.[2]

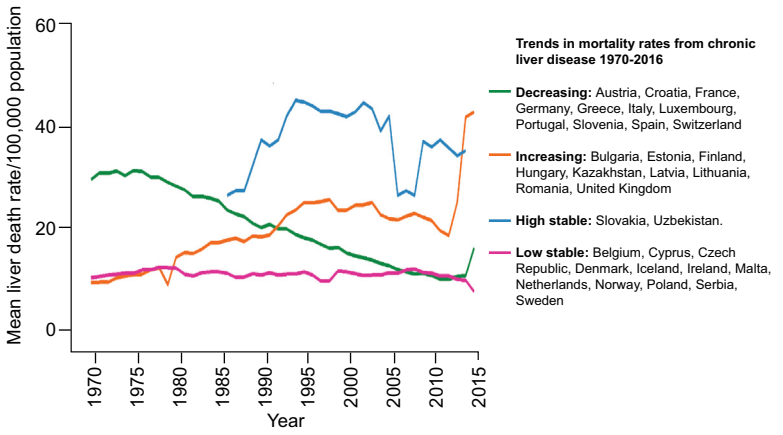

Fig. 2. Population-weighted average mortality rate for cirrhosis and other chronic liver diseases (excluding liver cancer) for European countries in four trend groups, 1970-2016. Data sourced from WHO Health for All Database.[172] Adapted with permission from the HEPAHEALTH project report.[16] WHO, World Health Organization. European Union member states were divided into four groups by the HEPAHEALTH report according to historical trends in liver-related mortality recorded between 1970 and 2016. [16] These were defined as follows: Decreasing trends: rates have dramatically decreased from very high rates in the 1970s; Increasing trends: rates have seen a sharp increase over 45 years; Low stable trends: rates remaining consistently below approximately 20 deaths per 100,000; High stable trends: rates remaining consistently above approximately 20 deaths per 100,000. Trends from 2012 should be treated with caution due to limited number of countries providing recent data.

Environmental factors

There are countless examples of how environmental and political factors have shaped liver mortality rates. In Finland, rapid substantial increases in liver mortality occurred in 2003 when Estonia joined the European Union (EU) and import controls were relaxed, leading to a flood of cheap alcohol.[27,28] An increase in alcohol tax and changes in alcohol availability curtailed the increase, and liver mortality.[15] The dissolution of the Soviet Union in the early 1990s saw the removal of restrictions on the alcohol trade in Eastern Europe, leading to a dramatic increase in overall consumption, particularly of poor quality strong home-brewed alcohol.[29] These events coincided with marked increases in cirrhosis mortality rates in the region, which remain high in Moldova and Hungary, where there is ongoing high consumption of hepatotoxic home-brewed fruit-based alcohol.[29] Within the UK, liver mortality has mirrored changes in alcohol affordability from reduced taxation, resulting in alcohol being 60% more affordable than in 1980.[15] This year-on-year increase only halted in 2008 following the introduction of the 2% above inflation duty escalator.

It is worth considering that environmental changes often harm high-risk drinkers to a greater degree than the population as a whole. While 70% of individuals within Europe drink some alcohol, only 6.4% of men and 1.2% of women are alcohol dependent.[30,31] The majority of patients with alcohol-related cirrhosis are heavy daily drinkers, with a median alcohol consumption of 120 units/week.[32] Furthermore the relationship between alcohol intake and cirrhosis is exponential for heavy drinkers, with a relative risk of 3 when consuming 20 units per week and 30 when consuming 80 units per week.[4,33] Therefore any increase in alcohol consumption by heavy drinkers, or an expansion of the size of this population driven by cheaper prices and increased

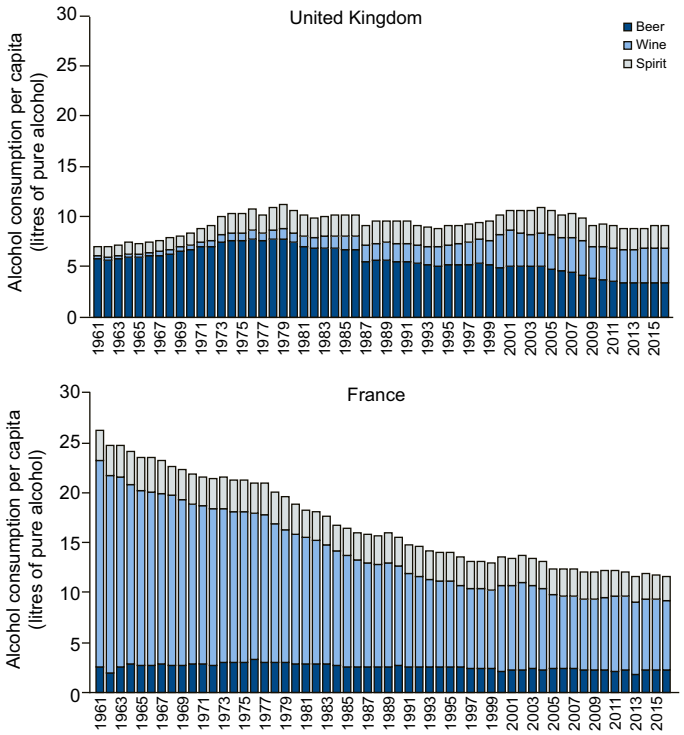

Fig. 3. Total consumption of alcohol by type of alcohol for individuals aged >15 years in the United Kingdom and France. Data from WHO Global Information System on Alcohol and Health.[26] WHO, World Health Organization.

availability, will directly result in elevated rates of cirrhosis and liver-related mortality. An increase in alcohol consumption by low-risk groups is unlikely to significantly impact these endpoints. However, for other harms like cancer where the relationship between consumption and harm appears linear, the impact of consumption changes in moderate drinkers are important.

Alcohol-related health inequalities

It has been consistently shown that mortality from ALD is substantially greater for individuals from more disadvantaged socioeconomic classes.[34,35] This is the case for all European countries, particularly in Eastern Europe, Finland and Denmark.[35] While the frequency and levels of consumption are increased in higher-educated groups in some European countries, high-risk drinking patterns leading to alcohol-related harm remain greater in more deprived populations.[36] Of concern, alcohol-related health inequalities are most evident in younger generations.[34] The shift of ALD from a disease of the rich in the 1930s, to a disease of the poor from the 1980s onwards is mirrored by the increasing affordability of alcohol, due to reduced taxation and deregulation.[15] The relative inequality of alcohol-related mortality has continued to increase over time as a result of a dramatic rise in alcohol-related deaths in lower socioeconomic groups.[35] In some European countries alcohol now accounts for at least 10% of the socioeconomic inequality in overall mortality.[35]

The wider burden of alcohol-related harm

Each year approximately 3.3 million deaths occur because of the harmful use of alcohol, corresponding to 5.9% of all deaths globally (7.6% males, 4.0% females).[37] Approximately one-quarter of deaths in 25–39 year olds are attributable to alcohol in the WHO European Region.[37] Alcohol accounts for 5.1% of the global burden of disease and injury as measured by disability-adjusted life years (DALYs), and leads to disability and death at a young age.[37] It moved from the eighth to the fifth most common cause of death and disability worldwide from 1990 to 2010.[38] In the UK alcohol is the leading risk factor for premature death and illness in individuals under 50.[10,39] Low-income countries and poorer populations have a greater disease burden per unit of alcohol consumption.[40]

Liver disease comprises less than 10% of the total burden of alcohol-related disease according to DALYs.[40] However, the prevalence and impact of alcohol-induced organ damage in extrahepatic tissues is largely unknown and deserves further research. Alcohol-related harms include cirrhosis, cancer (oesophageal, liver, colorectal, oropharyngeal, breast), hypertension, stroke, pancreatitis, neuropsychiatric disorders, unintentional injury, violence, suicide, maternal and perinatal disorders. Neuro-psychiatric disorders and unintentional injury account for approximately two-thirds of DALYs.[40] Additionally, the contribution of alcohol towards communicable diseases including human immunodeficiency virus, tuberculosis and respiratory tract infections is increasingly being recognised.[2] For individuals aged 15–49, tuberculosis, road injuries and self-harm were the leading causes of death attributable to alcohol, whereas for the over 50s this was cancer, accounting for 27.1% and 18.9% of alcohol-attributable deaths for women and men, respectively.[3] Importantly all aspects of alcohol-related harm are dose-related.[40,41] Aside from liver disease, the harmful effects of alcohol are poorly understood by the public. Of concern both the rates of hazardous drinking, associated with the greatest level of harm, and the rates of children consuming alcohol are increasing in many Organisation for Economic Co-operation and Development (OECD) countries.[6]

Harmful drinking is associated with costs beyond the individual, including the victims of road traffic accidents and violence and incalculable harm to families, as well as loss of productivity, social and health care costs and crime. Over two-thirds of individuals surveyed in Australia reported they had been adversely affected by someone else's drinking in the last year,[42] and data suggest women are more affected than men.[43] It is estimated that alcohol-related harm cost high-income countries an average of 2.5% of their gross domestic product (GDP).[40] In high-income countries the predominant cost was indirect due to productivity loss (72%), 13% was healthcare-related, 12% other direct costs and 3% for law enforcement.[40] As a comparison, the total economic cost of tobacco was estimated to be 2.2% of GDP for high-income countries in 2012.[44] Tragically around 40% of the total cost of alcohol misuse arises from the most deprived quartile.[45]

Key points

In Europe approximately 25% of deaths in 25–39 year olds are attributable to alcohol, which is associated with death and disability at relatively young ages.

Evidence for population level intervention

The WHO recommends 10 key and complementary areas for national action on alcohol that are evidence based (Box 1 and has set a voluntary target for nations of at least a 10% reduction in the harmful use of alcohol by 2025.[46,47] The WHO's "best buys" from this list (recommended to be undertaken immediately and deemed to be cost-effective, cheap, feasible and culturally acceptable) include population level approaches that involve governmental control: increasing alcohol excise taxes, restricting access to alcohol and implementing alcohol advertising bans.[48]

Governmental regulation of alcohol has a long global history. Examples can been found from Ancient and Imperial China where winemaking laws were repeatedly introduced then revoked (1100 BCE–1400 CE), Ancient Rome where Bacchanalia (alcohol-fuelled celebrations of Bacchus, the god of wine) were prohibited by the Senate (186 BCE)[49] and 18th century Great Britain where the

Box 1. World Health Organization target areas for national action on alcohol.[46,47]

(a) Leadership, awareness and commitment
(b) Health services' response
(c) Community action
(d) Drink-driving policies and countermeasures
(e) Availability of alcohol*
(f) Marketing of alcoholic beverages*
(g) Pricing policies*
(h) Reducing the negative consequences of drinking and alcohol intoxication
(i) Reducing the public health impact of illicit alcohol and informally produced alcohol
(j) Monitoring and surveillance

*WHO best buys.[48]

"Gin Acts" raised excise duties and limited licences for the sale of distilled spirits (1729–1751).[50] There is now an abundance of evidence, developed and published over the past 80 years,[51] that strongly supports a population level approach to reducing alcohol consumption and related harm.[24,52–54]

Pricing policies

Pricing policies have been evaluated more than any other alcohol control measure and are widely advocated to be among the first strategies that governments should implement to reduce alcohol-related harm, including liver disease.[6,30,55] Narrative reviews, systematic reviews and meta-analyses of studies on the effects of alcohol pricing strategies on alcohol consumption and alcohol-related morbidity and mortality at the population level have shown a consistent inverse relationship – when prices increase both consumption and harms decrease.[56–58] Wagenaar *et al.* found from 112 international studies that a 10% increase in price was associated with a 4.4% decrease in per capita consumption, and from 50 studies that a 10% increase in price was associated with a 3.5% decrease in alcohol-attributable mortality.[57,58] In light of this evidence, there are a range of pricing policy options available to governments and the most effective are outlined below.

Increasing alcohol excise taxes would both raise revenue for governments and reduce the associated health, social and economic costs of alcohol-related harm. At the very least alcohol excise taxes (as well as all other pricing policies) should be periodically adjusted for inflation to avoid alcohol becoming more affordable over time. Unfortunately, this is currently not the case in the US,[59] UK[60] or in most European countries.[61] In recognition that it is solely the volume of ethanol consumed (both episodically and cumulatively) that leads to alcohol-related harm, volumetric excise taxes are currently strongly advocated for by the public health community in developed nations such as the UK and Australia – where complicated taxation systems allow for very cheap alcohol to be sold *e.g.* white cider and spirits in the UK and cask wine in Australia.[62,63] Such volumetric taxes would be based on pure alcohol content (alcohol by volume) of beverages, thus limiting the availability of high-strength beverages at low prices.

Minimum pricing policies in various forms have been implemented in the 10 Canadian provinces,[64] Russia, Republic of Moldova, Ukraine, Uzbekistan[65] and most recently Scotland.[66] In general they limit the availability of low-cost alcohol through a set floor price below which alcoholic beverages cannot be sold. Comprehensive evaluations in areas of Canada, where minimum pricing has been in place for several decades, found that a 10% increase in minimum price was associated with an 8.4% decrease in alcohol consumption[7] and a 32% decrease in alcohol-attributable mortality.[67] In low-income areas a 10% increase in minimum price was associated with a 35% decrease in hospitalisations for acute alcohol-attributable conditions compared with a decrease of 9% and 6% in medium-income and high-income areas, respectively.[68]

The concept of a minimum pricing model commonly known as minimum unit price (MUP) first gained traction around 2008.[69] MUP has been posited as the best model of minimum pricing as it ensures that no types of alcoholic beverages can be sold below a set price and it targets the heaviest drinkers who gravitate towards cheap high-strength alcohol.[70] It is also recommended that it should be implemented in combination with volumetric taxation.[62,63] MUP modelling has been undertaken by the Sheffield Alcohol Research Group to estimate the likely positive health, social and economic effects across the UK and Republic of Ireland.[71–73] The UK government committed to introducing a MUP in England and Wales in their 2012 alcohol strategy,[74] however, it reversed its decision the following year claiming an absence of empirical evidence to support the measure.[75] The Scottish government led the way and legislated for a MUP in 2012.[76] It took 6 years of continued legal challenges by the alcohol industry for MUP to become a reality in Scotland, where it was implemented on 1st May 2018, set at 50 pence per unit of alcohol (8 mg of ethanol).[66,77] The governments of the other constituent countries of the UK and Ireland have been watching the Scottish example with interest and legislation for MUP was passed in Wales in June 2018.[78] Evaluations of these ground breaking natural experiments, both government and independent studies, will be available in time.[79]

Key points

At the population level, there are a range of pricing policy options, which have been shown to reduce alcohol consumption and alcohol-related harm.

Restricting access to alcohol

During the 1970s there was a trend across the US of reducing the legal minimum purchase age of alcohol from 21, followed by a trend in the

1980s of increasing it again due to a federal government incentive. These changes in the US, similar changes in Canada, and decreases in purchase age in Australia and New Zealand, provided researchers with a multitude of natural experiments to study. There is strong evidence that decreases in the legal minimum purchase age for alcohol are associated with increases in youth drinking and road traffic accidents among young people. Similarly, there is an inverse association for these outcome measures when minimum purchase ages are increased.[80–84]

The next area where there is evidence for restricting access to alcohol is restricting the trading hours of licensed venues. Systematic reviews of the international literature have concluded that extended trading hours for both on- and off-licences are associated with population level increases in alcohol-related harm, particularly injuries, and restricted trading hours are associated with decreases in alcohol-related harm.[85–91] The majority of studies in these reviews are from natural experiments in Australia and the UK. When trading hour restrictions were relaxed following a change to the Licensing Act in England and Wales in 2003, allowing for up to 24 hour trading, the evidence base available at the time had not been followed.[92–94] Evaluations of this policy change have not shown as consistent results when compared to those from Australia, Canada and the US.[88]

Restricting licensed outlet density does not have as strong an evidence base as that of minimum purchase age or trading hours. Natural experiments are relatively rare as numbers of outlets usually increase gradually over time rather than rapidly following a policy change. Controlled before and after designs (the strongest study design when randomised controlled trials are not feasible) have only been undertaken in a small number of cases, therefore, the bulk of the evidence comes from longitudinal and cross-sectional studies. The quality of studies in this research area is mixed as well as the findings.[95,96] Systematic reviews of the available evidence, mostly studies from the US and an increasing number from Australia, have concluded that increased numbers of licensed outlets in communities are likely to be associated with increases in alcohol-related harm in communities – the strongest association being between outlet density and violence.[86,89,91,96,97]

Regulating advertising

Studies relating to the effects of alcohol advertising on alcohol consumption have mainly focused on young people under the legal minimum purchase age. Systematic reviews of the international literature, including experimental and longitudinal study designs, have concluded that exposure to alcohol advertising by youth is associated with initiation of drinking, increased drinking and binge drinking.[98–103]

The alcohol industry invests substantially in advertising – over £5 billion a year (15% of annual revenue) for the leading global alcohol company[104] – which is a clear indication of the importance of this strategy in boosting sales and shareholder profits. Advertising online through social media is a growth area with international reach,[105] however, nearly half of countries report no restrictions on advertising through this medium, indicating that regulation in this area is failing to keep up with technological advances.[2] Furthermore, alcohol advertising pervades international sports competitions such as the Soccer World Cup.[106] The most common model of alcohol advertising regulation is self-regulation by the alcohol industry.[107] There is evidence of this system failing to protect youth from alcohol advertising exposure[108,109] and in some cases advertising appears to actively target youth.[110,111] There are coordinated calls for government regulation of alcohol advertising and even complete bans.[55,112,113] It is important to note that there have been few evaluations of such models and at present little evidence to support or reject their effectiveness,[114] however, the self-regulatory model is failing.

Raising public awareness

The international evidence for sustained individual behaviour change stemming from school-based education programmes, warning labels on alcoholic beverages, low-risk drinking guidelines and large scale public health campaigns is relatively weak,[115–117] however, they remain the most popular prevention strategies employed by governments and unsurprisingly have strong support from the alcohol industry.[118,119] Raising public awareness of the links between alcohol consumption and the wide ranging negative health, social and economic impacts and providing guidance on levels of health risk associated with different levels and patterns of consumption is very important, but it needs to be a component of a multi-pronged strategy that also addresses the price, access to and promotion of alcohol.

Evidence for individual interventions

Screening and brief interventions

The majority of individuals with alcohol-related liver fibrosis have normal liver blood tests.[120,121] Therefore, early identification and management of individuals with ALD is reliant on screening for alcohol misuse followed by a brief intervention. A number of screening tools exist and algorithms vary between countries. The British Society of Gastroenterology and British Association for the Study of Liver disease have recently published guidelines which suggest that individuals with "harmful drinking patterns" (greater than

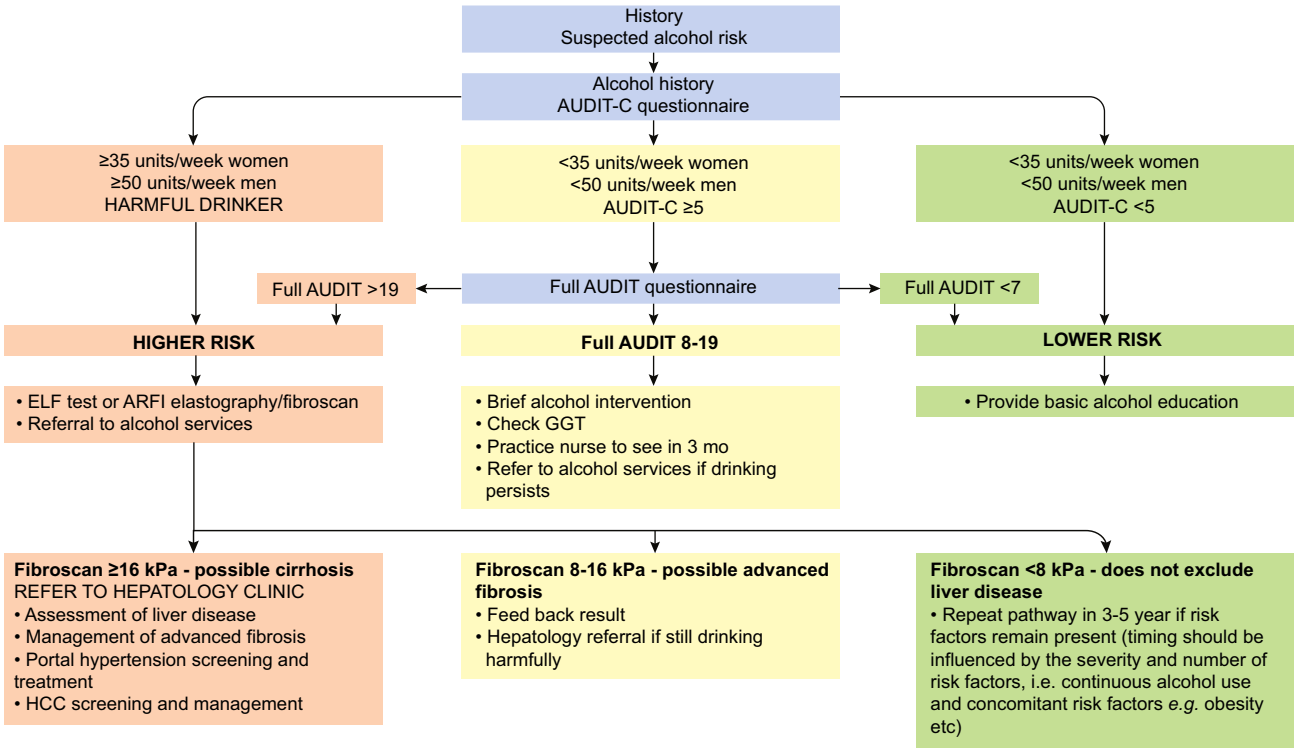

Fig. 4. Diagnostic pathway for the detection of alcohol-related liver disease in the community. Adapted with permission from *Gut*.[123] ARFI, acoustic radiation force impulse; ELF, enhanced liver fibrosis; GGT, gamma-glutamyltransferase; HCC, hepatocellular carcinoma.

50 units per week for men and 35 units per week for women) are screened for cirrhosis using transient elastography (TE) or liver fibrosis markers (Fig. 4).[122–124] Similarly, the UK's National Institute of Health and Care Excellence (NICE) recommend that all young people and adults (aged 16 +), drinking at these levels for several months are offered non-invasive testing for cirrhosis in the form of TE, and are re-tested for cirrhosis every 2 years where a diagnosis of ALD has been made.[124,125] For people drinking less than this, initial screening can be performed using the 3 item Alcohol Use Disorders Identification Test (AUDIT)-C score, which is effective at identifying high-risk drinkers who may not be alcohol dependent, followed by the full 10 item AUDIT screening for individuals scoring greater than or equal to 5 (Fig. 4).[122–124] AUDIT-C is more sensitive than the CAGE questionnaire for detecting heavy drinking and better identifies current harmful drinking patterns.[126]

A brief intervention involves providing feedback on an individual's alcohol use and any associated harm (Box 2). This is delivered in a single short encounter with a health care professional. Even simple advice leaflets are effective.[127] The goal is to reduce harmful and hazardous drinking patterns associated with harm, rather than abstinence. Screening followed by a brief intervention is one of the most effective and cost-effective alcohol policies for addressing hazardous and harmful drinking at the individual level, as identified by the OECD model and others.[6,52] They are particularly influential in primary care.[128–135] Numbers needed to treat to stop harmful drinking are between 1:8 and 1:12. A UK model suggests that delivery of a brief intervention to every patient registering with a new general practitioner would lead to a reduction of 2,500 alcohol-related deaths and 125,000 hospital admissions over 20 years, associated with a cost saving of £282 million.[136] Individuals in the lowest socioeconomic groups were predicted to experience the greatest relative reduction in harm. To improve the impact of brief investigations, further research is needed to understand their effectiveness in groups other than middle-aged men (*i.e.* women, young drin-

Key points

Alcohol use screening followed by a brief intervention is one of the most effective policies for tackling hazardous and harmful drinking at the individual level.

Box 2. Brief Intervention Components (adapted from Public Health England Review: The Public Health Burden of Alcohol and the Effectiveness and Cost-Effectiveness of Alcohol Control Policies).[173]

- Clarification regarding what constitutes low-risk consumption
- Information on the harms associated with risky alcohol use
- Benefits of reducing intake
- Motivational enhancement to support change
- Analysis of high-risk situations for drinking
- Coping strategies and the development of a personal plan to reduce consumption

Box 3. Alcohol care team model.[4]

- A consultant-led, multidisciplinary, patient-centred Alcohol Care Team, integrated across primary and secondary care
- A seven-day alcohol specialist nurse service
- Co-ordinated policies for the emergency department and acute medical units
- A rapid assessment, interface and discharge (RAID) liaison psychiatry service
- An alcohol assertive outreach team for frequent attenders
- Formal links with local authority, community care groups, public health and other stakeholders

kers, ethnic minorities), their optimum content and the longevity of the interventions effect.

Screening for biochemical evidence of liver disease in the community increases the impact of brief interventions, while reducing both hospital admissions and mortality.[120,137] The Malmo study found that informing high-alcohol consumers of a raised gamma-glutamyltransferase (GGT) improved outpatient attendance where a brief intervention could be delivered.[137] Interventions delivered via computers and smart phones can also reduce alcohol consumption in hazardous and harmful drinkers.[138] In the hospital setting, a recent study has shown it is feasible to screen all medical admissions to identify individuals at risk of alcohol abuse, to prompt an early brief intervention or referral to an alcohol specialist nurse.[139] Once admitted, alcohol advice delivered by a liver specialist can lead to a high proportion of patients reducing their intake.[9] Dedicated alcohol care teams are also highly effective at reducing future hospital admissions, primary care attendance and improving quality of life.[131,140,141] These findings led the Lancet Commission to propose an alcohol care team model in 2014 (Box 3).[4] Patients and relatives are likely to be highly susceptible to health messages while experiencing an episode of alcohol-related harm and a consistent message delivered by a wide range of health care professionals is extremely valuable.

Pharmacological interventions

A wealth of evidence supports the efficacy of pharmacological treatments in combination with psychosocial support to promote abstinence, reduce alcohol consumption and prevent relapse.[142] Approved agents are summarised in Table 1. There is no clear evidence of how long these medications should be continued, although 6 months is suggested for patients with a good response.

Non-invasive diagnostic tools to detect liver fibrosis in the community secondary to alcohol

Liver disease is silent prior to decompensation, by which point 1-year survival rates are low. Nearly 75% of individuals with liver disease present for the first time with a non-elective hospital admission and end-stage disease (Fig. 5).[4] While abstinence in late disease leads to dramatic improvements in portal pressure and histology, a third of patents die before their liver recovers.[9] It is therefore vital to detect liver disease early enough to allow lifestyle changes to impact mortality. Being informed of an early diagnosis of liver disease leads two-thirds of harmful or dependent drinkers to stop.[130]

Detecting early fibrosis in the context of alcohol is a developing field. Up to 90% of individuals with early alcohol-related fibrosis and 75% with severe fibrosis have normal standard liver blood tests.[120,121] An aspartate aminotransferase (AST): alanine aminotransferase ratio of greater than 2 can be indicative of advanced ALD, but is also increased if examined shortly after recent heavy alcohol exposure; this ratio also has low levels of sensitivity and specificity in this setting.[143] A raised GGT, while having a low specificity for liver disease, is one of the best predictors of the presence of significant liver disease and liver-related mortality within the community.[144,145]

TE is currently the gold standard to detect cirrhosis for individuals with any risk factor for liver disease, including those drinking at harmful levels.[4,123,124] While there is some evidence that recent heavy alcohol consumption and alcoholic hepatitis may lead to increases in liver stiffness, influencing the cut-off points for different degrees of fibrosis, many of these studies did not control for random variations in non-drinkers and AUROC values remain extremely high for detecting advanced fibrosis and cirrhosis.[146–148] In the context of alcohol excess, TE outperforms, or is comparable to, all commonly used non-invasive serum fibrosis markers,[149,150] and has achieved AUROC values in the range of 0.90 to 0.97 for detecting F ≥3 fibrosis in prospective studies.[149–151] Furthermore, liver stiffness values obtained using TE significantly correlate with hepatic venous pressure gradients.[152] In common with other non-invasive investigations, TE more accurately excludes severe fibrosis and cirrhosis rather than early fibrosis,[148,153] with negative predictive values for detecting F ≥3 and F = 4 fibrosis found to be 72% and 87%, respectively, compared to 38% and 49% for F ≥1 and F ≥2 fibrosis.[148]

The Enhanced Liver Fibrosis (ELF) score is determined by an algorithm derived from 3 serum biomarkers, procollagen 3 N-terminal peptide, hyaluronic acid and tissue inhibitor of metalloproteinase 1, and has been found to be predictive of clinical outcomes including liver-related mortality.[154] A score of greater than 10.51 suggests advanced fibrosis. While only 64 patients with ALD were included in the original study of 1,021 individuals, AUROC values were 0.944, compared to 0.870 (non-alcoholic fatty liver disease) and 0.773 (hepatitis C),[155] and 0.92 in a recently

Table 1. Summary of approved pharmacological agents used to reduce harmful alcohol consumption.

Treatment	Mechanism of action	Role	Summary of evidence	Cost-effectiveness	Notes
Acamprosate	Glutamate antagonist	Reduce alcohol cravings in long term heavy alcohol consumers.	19 RCTs (>4,600 participants) acamprosate *vs.* placebo. Acamprosate was better at promoting abstinence in participants, RR = 0.83 (0.77–0.88)[142]	Compared with standard care, acamprosate resulted in net healthcare savings of about £68,900. This finding was mirrored by a German study.[142]	Has not been tested in patients with cirrhosis. Avoid if creatinine >120 μmol/L.
Naltrexone	Opiate antagonist	Reduce alcohol cravings, reduce heavy drinking episodes and frequency of consumption.	27 RCTs (nearly 4,300 participants), naltrexone *vs.* placebo. Naltrexone more effective at increasing the percentage days abstinent at 3 months follow-up SMD = −0.22 (−0.37 to −0.07).[142]	Naltrexone was associated with a net economic cost of £83,400 compared with standard care in a UK study, but has been found to be cost-effective in an Australian study (ICER AUS$13,000) and when provided in combination with acamprosate.[142]	Has not been tested in patients with cirrhosis.
Disulfiram	Inhibits the oxidation of alcohol at the acetaldehyde stage (aldehyde dehydrogenase)	Causes an alcohol hypersensitivity reaction (aversion therapy).	3 open-label trials (859 participants), disulfiram *vs.* placebo. Disulfiram was more effective at increasing the total number of abstinent days, SMD = −0.45 (−0.86 to −0.45).[142]	Possible net economic costs in comparison to standard care, although there is a large discrepancy between studies.[142]	Due to risks of hepatotoxicity should be avoided in severe ALD.[165]
Nalmefene	Opioid antagonist	Adults drinking at high risk levels (>60 g/day men, >40 g/day women) with mild dependence without withdrawal symptoms, not requiring immediate detoxification.	5 RCTs (over 2,500 participants), nalmefene + psychosocial support *vs.* placebo, + psychosocial management. Nalmefene reduced the number of heavy drinking days and total alcohol consumption.[166] However, differences disappeared when allowing for the increased number of withdrawals from the nalmefene group due to safety reasons and there were no differences in health outcomes between the groups at 6 months and 1 year.[166]	Modelling of nalmefene + psychosocial support *vs.* psychosocial support alone: i) More cost-effective; ii) Averted 4,900 alcohol-related disease and injuries and 250 deaths/100,000 patients at 5 years; iii) Large gain in QALY (0.071 QALYS); iv) When applying the upper estimate for no. medical visits per month, the ICER increases to £6,274 per QALY gained[167]; v) However, these studies were not powered to examine the efficacy of nalmefene in the subgroup for which it is licenced and there are no trials comparing nalmefene with another active drug.[168]	
Baclofen	Gamma-aminobutyric acid $(GABA)_B$ receptor agonist	Promote abstinence in selected patients.	12 RCTs, baclofen *vs.* placebo. Baclofen more effective at inducing abstinence (OR 2.67; 95% CI 1.03–6.93; $p = 0.04$; NNT 8). No reduction in heavy drinking days or cravings. Substantial heterogeneity across studies. Not universally effective.[169]	Not as yet comprehensively assessed.	Temporary licence in France only. Only alcohol pharmacotherapy tested in individuals with significant ALD.[170]

ALD, alcohol-related liver disease; ICER, incremental cost-effectiveness ratio; NNT, numbers needed to treat; OR, odds ratio; QALY, quality adjusted life years; RCT, randomised control trial; RR, relative risk; SMD, standardised mean difference.

published study in patients with ALD alone.[150] The ELF score has a high sensitivity and low false negative rate and is useful as a screening test within primary care.[150,155,156] The FibroTest, FibroMeter™ and HepaScore achieve similar sensitivities and specificities to that of FibroScan® where low and high cut-offs are used to exclude fibrosis, or diagnose cirrhosis, respectively.[157–159] The APRI (AST to platelet ratio index) and Forns scores both achieve low AUROCs in ALD.[159,160] As yet no benefit has been shown when combining serum non-invasive fibrosis markers, or using these in combination with FibroScan.[150,159]

Looking forward

Despite the overwhelming evidence that alcohol-related public health policies can prevent substantial numbers of premature deaths at a population level, reduce economic costs and improve inequality, policymakers have failed to react and continue to be strongly influenced by industry. Less than half of countries have imposed a MUP, adjusted taxes according to inflation and income levels, or banned volume discounts.[2] Total per capita alcohol consumption worldwide has failed to decrease since 2010, with intake expected to increase over the next decade.[2] The EU alcohol strategy (2006–

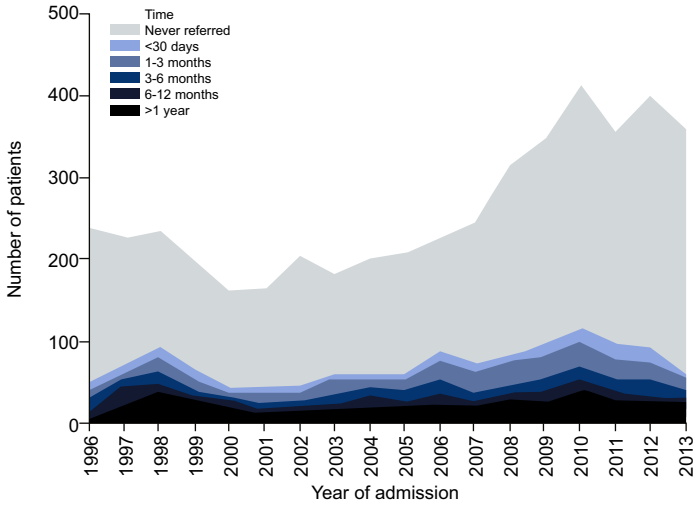

Fig. 5. Time period between referral to a liver clinic and the first admission with cirrhosis or liver failure. Adapted with permission from *Clinical Medicine*.[4]

12) made commitments to measure alcohol-related harm and consumption, promote regulation at a national level and bring health experts and the drinks industry together to pledge voluntary actions to reduce alcohol-related harm, with a plan to introduce effective regulation if this was insufficient.[161,162] After 6 years the health community disengaged when it became clear the commission was not prepared to implement effective policies. The policy ended with no objective evidence that any alcohol-related deaths had been prevented. An enquiry concluded the EU should have concentrated on what it could enforce above the agendas of individual member states.[163] Major areas for reform include the current EU alcohol taxation regime which prevents member states from increasing tax on the most harmful substances, and the inclusion of alcoholic drinks within the EU food labelling legislation to include strength, calorie content and guidelines on safe drinking. It was agreed voluntary commitments are not sufficient.

The French model has taught us that a switch from quantity to quality can both reduce alcohol-related harm and increase returns for drinks company shareholders. Instead short-term agendas have led the alcohol industry to simply push to expand the market through price reductions and advertising, particularly targeted at young people. Their ability to lobby governments with arguments regarding the "nanny-state" and anti-business agendas neglects the health and social needs of that community or population; yet the increasing multi-national nature of the alcohol industry (a single company currently controls around one-third of the global beer market),[164] gives it great strength to influence governments.

Ultimately a significant reduction in global alcohol-related harm will require coordinated leadership and action internationally, for example the inclusion of alcohol-related targets in the 2030 Agenda for Sustainable Development and other major global policy and strategic frameworks, involvement of the United Nations and other major political unions including the EU, as well as at a governmental level.[2] However, clinicians can make a huge impact by looking outside the hospital, engaging with local media and policy-makers, inviting them to see patients, discussing the burden of alcohol-related harm and evidence-based policies. Voluntary organisations led by clinicians, non-government organisations and patients, such as the UK Alcohol Health Alliance and Scottish Health Action on Alcohol Problems have been extremely influential at changing policy at a national level. There are currently no effective treatments for ALD and most patients present too late to change their outcome, but ALD is preventable at its early stages. Therefore, hepatologists need to re-focus on this key time for their patients, engaging as leaders in public health locally and nationally to positively influence this hugely preventable disease burden for future generations.

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Conflicts of interest

There are no conflicts of interest to declare.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

T. Hydes and W. Gilmore drafted the manuscript, which was reviewed by N. Sheron and I. Gilmore.

Supplementary data

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