THE LANCET

Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis

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Executive summary

Liver disease in the UK stands out as the one glaring exception to the vast improvements made during the past 30 years in health and life expectancy for chronic disorders such as stroke, heart disease, and many cancers. Mortality rates have increased 400% since 1970, and in people younger than 65 years have risen by almost five-times. Liver disease constitutes the third commonest cause of premature death in the UK and the rate of increase of liver disease is substantially higher in the UK than other countries in western Europe. More than 1 million admissions to hospital per year are the result of alcohol-related disorders, and both the number of admissions and the increase in mortality closely parallel the rise in alcohol consumption in the UK during the past three decades. The new epidemic of obesity is equally preventable. Of the 25% of the population now categorised as obese, most will have non-alcoholic fatty liver disease and many (up to 1 in 20 of the UK population) will have ongoing inflammation and scarring that finally leads to cirrhosis. Of those patients with cirrhosis, 5–10% will get liver cancer. This increasing burden of liver disease is added to by chronic viral hepatitis; annual deaths from hepatitis C have almost quadrupled since 1996 and about 75% of people infected are estimated to be still unrecognised. The same applies to chronic hepatitis B infection, in which progression to cirrhosis and liver cancer also happens. The number of silently infected individuals in the UK is increasing every year as a result of immigration from countries with a high prevalence of hepatitis B and hepatitis C infections.

Costs to the UK's National Health Service are equally staggering, with estimates of £3·5 billion per year for alcohol-related health problems and £5·5 billion per year for the consequences of obesity. Obesity costs are almost certainly an underestimate now that the disorder is recognised as an important factor in several common cancers, including breast cancer and colon cancer.[1] Obesity is a factor in metabolic disorders—the basis of diabetes, hypertension, cardiac diseases, and strokes. Furthermore, the poorest and most susceptible in society have the highest incidence of liver disorders, making liver disease a major issue for health inequalities.

Of particular concern is the 2013 National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report,[2] which showed that the care of patients acutely sick with liver disease dying in hospital was judged to be good in less than half of patients; other unacceptable findings were the inadequate facilities and lack of expertise of those caring for patients. Also, it is increasingly evident that deficiencies exist in primary care, which has crucial opportunities for early diagnosis and prevention of progressive disease.

The aim of this Commission is to provide the strongest evidence base through involvement of experts from a wide cross-section of disciplines, making firm recommendations to reduce the unacceptable premature mortality and

Lancet 2014; 384: 1953–97

Published Online
November 27, 2014
http://dx.doi.org/10.1016/S0140-6736(14)61838-9

This online publication has been corrected. The corrected version first appeared at thelancet.com on December 19, 2014

See Editorial page 1902

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Key messages: Ten key recommendations

1. Strengthen detection of early liver disease and its treatment by improving the level of expertise and facilities in primary care
2. Improve support services in the community setting for screening of high-risk patients
3. Establish liver units in district general hospitals to be linked with 30 specialist centres regionally distributed, for availability of highly specialised investigations and treatment
4. A national review of liver transplantation services to ensure better access for patients in specific areas of the country; provide sufficient capacity for the anticipated increase in availabilty of donor organs
5. Strengthen continuity of care in transition arrangements for the increasing number of children with liver disease surviving into adult life
6. Implement a minimum price per unit, health warnings on alcohol packaging, and restriction of alcohol advertising and alcohol sales
7. Promotion of healthy lifestyles to reduce obesity in the country and its results on health; governmental regulations to reduce sugar content in food and drink; use of new diagnostic pathways to identify people with non-alcoholic fatty liver disease
8. Eradication of infections from chronic hepatitis C virus in the UK by 2030 using antiviral drugs; reduce the burden of hepatitis B virus; target high-risk groups for these viruses, including immigrant communities; use of a universal six-in-one vaccination for infants for hepatitis B
9. Increase provision of medical and nursing training in hepatology and wider educational opportunities for health-care professionals to increase the number of doctors and nurses in hospitals and primary care
10. Increase awareness of liver disease in the general population with a national campaign led by National Health Service (NHS) England; clinical commissioning groups increase awareness in area health teams

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disease burden from avoidable causes and to improve the standard of care for patients with liver disease in hospital. From the substantial number of recommendations given in our Commission, we selected those that will have the greatest effect and that need urgent implementation. Although the recommendations are based mostly on data from England, they have wider application to the UK as a whole, and are in accord with the present strategy for health-care policy by the Scottish Health Boards, the Health Department of Wales, and the Department of Health and Social Services in Northern Ireland.

Our ten key recommendations are based on the strong evidence base and are in line with reports in 2014 of several other enquiries, including from the 2014 All Party Parliamentary Group on Hepatology[3] and the All Party Parliamentary Group on alochol misuse. Results showing the value of a minimum unit price policy in targeting heavy drinkers were published in *The Lancet* in May, 2014, and the European Observatory on Health Policy, together with the Department of Health and NHS England, has drawn attention to four areas of premature mortality, including liver disease, in which the UK lags behind other European countries. Such stark contrasts with our European neighbours are unacceptable and in this Commission we give clear, evidence-based policy proposals for the UK Government to use in closing the gap in liver disease.

Introduction

This Commission was set up after the meeting (*Addressing the Crisis in Liver Disease in the UK: alcohol, viral hepatitis and obesity*) by the Foundation for Liver Research to highlight the serious situation emerging with respect to liver disease in the UK. Held on July 15, 2013, the meeting was timely because it was a few weeks after the report *Hospital Deaths from Alcohol-related Disease* was released by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) containing alarming statistics, including care being rated as less than good for more than half of patients with liver disease. UK Government ministers had also announced in July, 2013, that they were not proceeding with the minimum unit price proposal for targeting heavy drinkers, which was the cornerstone of their previously published alcohol strategy to bring down levels of overall alcohol consumption in the country. However, the present Secretary of State for Health, Jeremy Hunt, had announced a campaign to reduce levels of premature mortality in the country, of which liver disease was listed third of the so-called Big Five causes

In his mandate to the Commission, Richard Horton, editor of *The Lancet*, stressed the need for the recommendations to be evidence-based and scientifically focused. He suggested the inclusion of experts from a wide cross-section of disciplines and said that economic considerations were crucial bearing in mind the financial pressures on the UK's National Health Service (NHS).

Our Commission describes the extent of the problem of liver disease in terms of mortality rates, numbers of hospital admissions, the present deficiencies both in hospital and primary care settings, and the association between the burden of liver disease and social deprivation in the UK. We provide a blueprint for improving hospital care, with accreditation at two levels—acute district general hospital liver units providing 7-day acute services for emergency care and regional specialist centres—that would be responsible for more specialised investigations and care including liver transplantation.

We report about the rapidly rising levels of obesity in the country, and the results in terms of non-alcoholic fatty liver disease and the continuing high burden of alcoholic liver disease, which largely account for the unacceptable figures of premature mortality. We also consider chronic viral hepatitis B and C and their role in liver disease because the potential now exists for eradicating these infections with the licensing of new and highly effective antiviral drugs.

We then discuss the need to obtain greater engagement of primary care in the early detection and treatment of liver disease, highlighting the present poor understanding of liver disorders and describing practical measures to correct this based on the availability of more appropriate blood test investigations, along with a new care-management pathway.

We also point out the excellent outcomes for biliary atresia and other childhood liver diseases being obtained in the three national specialist centres and the need for an even greater public awareness of the importance of early diagnosis.

Our Commission provides an economic analysis of the costs of liver disease and the potential savings obtainable through upscaling of preventive and treatment services, and by reduction in unnecessary referrals to hospital.

In the last section, we consider the new commissioning arrangements and public interface with respect to increasing the awareness of liver problems and the bringing together of specialist societies, liver charities, and patients in implementation of the recommendations of our Commission.

We have ten key recommendations that have been selected for strong endorsement and need to be urgently implemented.

Extent of liver disease in the UK

In the past few decades vast improvements have been made in health, and death rates have decreased for almost all diseases. In some areas (eg, cardiac disease), in which large health resources have been invested, the decrease in mortality has been substantial. Liver disease is the exception; standardised mortality rates have increased 400% since 1970, and in patients younger than 65 years have increased by almost 500% (figure 1). Most patients die in working age (18–65 years) and as a result, according to the Office of National Statistics, liver disease is the third biggest cause of premature mortality with 62 000 years of working life lost every year. Only ischaemic heart disease (74 000 years) and self-harm (71 000 years) lead to a greater premature loss of life[5] and indeed, liver disease was included in the so-called Big Five targets announced by the Health Secretary for reduction of premature mortality.[6] In England and Wales 600 000 people have some form of liver disease of whom 60 000 people have cirrhosis, leading to 57 682 hospital admissions and 10 948 deaths in 2012.[7] These figures represent increases of 62% in liver disease and 40% in cirrhosis in 10 years.[7] Every year, admissions to hospital because of liver disease increase, with most patients being admitted with serious end-stage disease, liver cirrhosis, or liver failure. Three-quarters of deaths from liver disease are the result of excess alcohol consumption; deaths caused by other lifestyle risk factors of obesity and viral hepatitis are also increasing. This increase does not take into account the number of acute and chronic pancreatitis cases (45 000 admissions each per year) and the effect on cardiovascular disease (at least 50% of attributable fractions of alcohol-related admissions to hospital), or the emerging problem of alcohol-related brain damage on hepatology wards.[8] Liver health is a barometer for the wider health environment and a reminder that lifestyle-induced (ie, non-communicable) disease is the major challenge for global health in the 21st century.[9]

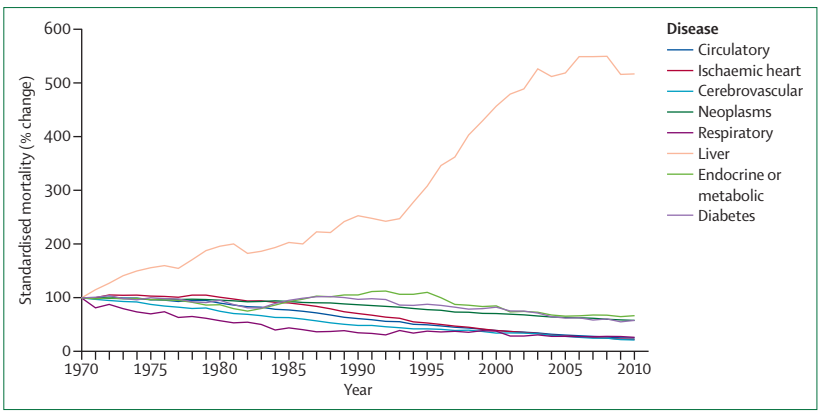

***Figure 1*: Standardised UK mortality rate data**
Data were normalised to 100% in 1970, and subsequent trends plotted using the software Statistical Package for the Social Sciences. Data are from the WHO-HFA database.[4] Analysed by Nick Sheron (September, 2013).

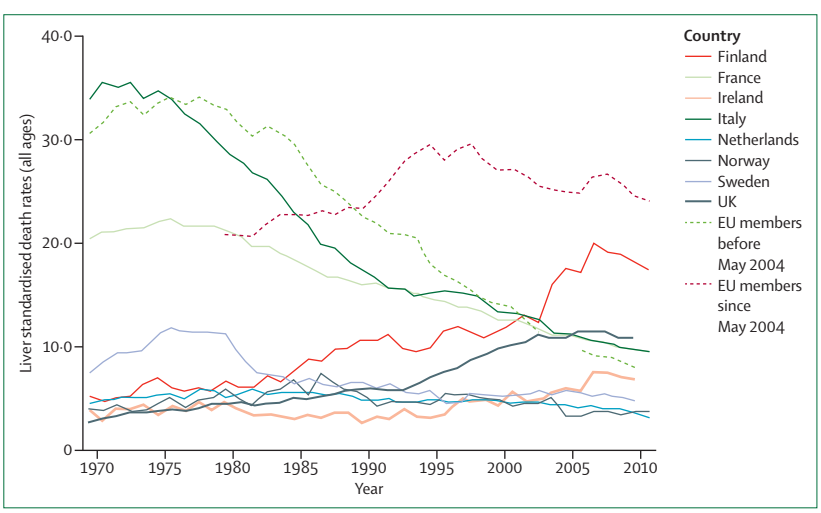

***Figure 2*: Standardised liver death rates in countries in the European Union before 2004**
Decrease in liver mortality in selected European Union countries compared with UK mortality. Data are from the WHO-HFA database.[4] Analysed by Nick Sheron.

By contrast with the trend of liver mortality in the UK, the opposite has happened in much of western Europe (figure 2). In 1960, liver mortality in France was 50 in 100 000 population, 25 times higher than in the UK at the same time. The French health services were prepared to deal with liver disease at every level, from specialist liver units to the widespread use of simple non-invasive diagnostic techniques for detection of early disease.[10] Innovative alcohol policies, including controls on marketing such as the 1991 *Loi Evin* law (the prohibition of alcohol adverts on television and cinemas and inclusion of a warning on bottles stating that alcohol is dangerous to your health), were introduced and the consumption of cheap strong alcohol (wine in this case) decreased,[11] further showing that reduction in population

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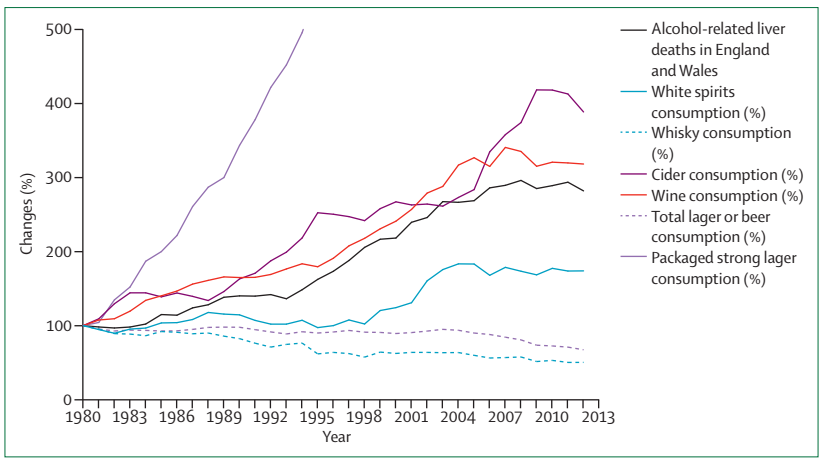

Figure 3: **Changes in the UK alcohol market, 1980–2013**
Alcohol-related liver deaths for England and Wales were taken from Office of National Statistics Deaths Registered series,[15] consumption data are from HMRC collated in the British Beer and Pub Association Handbook.[16] Comparing liver mortality with consumption of white spirits, wine, cider, and strong lager shows R^2=0·987, p<0·0001. Analysed by Nick Sheron (May, 2014).

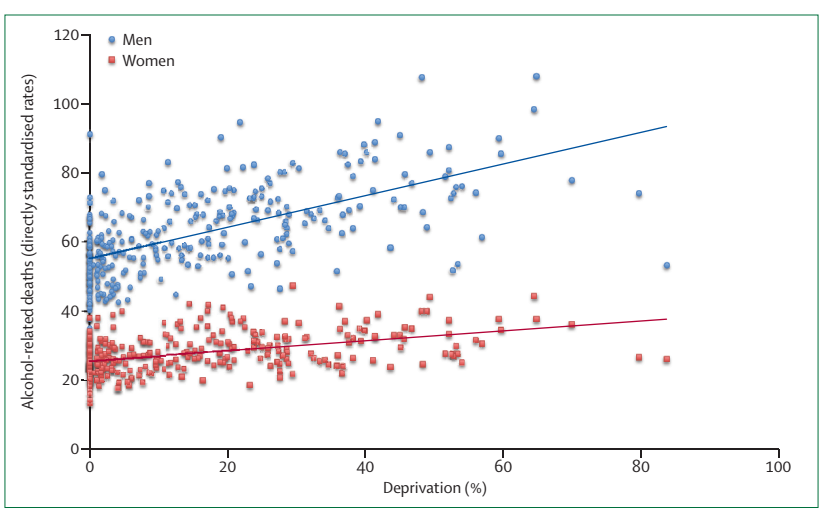

Figure 4: **Alcohol-related deaths, directly standardised rates, for 2012 at local authority geography**
Data were taken from the Local Alcohol Profiles for England.[20] Deprivation is calculated as percentage of 2010 local authority population living in the most deprived national quintile.[21] Although relationships between deprivation and alcohol related mortality are highly significant for both men and women, the relation is stronger and steeper for men (R^2=0·386, p<0·0001) than for women (R^2=0·188, p<0·0001).

For more on **Alcohol Misuse from the All Party Parliamentary Group** see http://www.alcoholconcern.org.uk/what-we-do/appg-on-alcohol-misuse/

levels of alcohol consumption is the most effective way to reduce overall mortality from liver disease.[12] The UK overtook France, Italy, and Spain in terms of liver mortality in the 1990s and only Finland, where availability of alcohol has been liberalised as in the UK, has had a similar upward trend in liver mortality.

Alcohol-related deaths correlate with alcohol consumption at the population level[13] and are fuelled by cheap strong alcohol.[14] The increase in hospital admissions and mortality in the UK is largely accounted for by increased levels of consumption in past decades. Alcohol consumption has shifted substantially from moderate strength beer sold in pubs, to strong lager, cider, wine, and spirits sold by supermarkets for drinking at home (figure 3). Taxation has not kept pace with increased incomes and the resulting increased affordability of alcohol has affected most severely on very heavy drinkers and young people. Around a quarter of the UK population drink more than the recommended guideline amount (hazardous drinkers) with 10% of the population drinking even more than this (harmful drinkers), but these hazardous and harmful consumers account for three-quarters of alcohol sales.[17] As noted by the House of Commons Health Committee, "The alcohol industry should not carry more weight in determining health policy than the Chief Medical Officer".[18]

A third of patients with alcohol-related liver disease have severe alcohol dependency or alcoholism[19] and roughly 20–30% of lifelong heavy drinkers develop cirrhosis. Two crucial factors emphasise the importance of the harmful effects from alcohol on the liver and on wider aspects of health in the UK, both of which should be considered in present government policies. First, alcohol causes premature avoidable death and is the biggest risk factor for death in men younger than 60 years. Second, a strong social trend exists in alcohol-related death with the poorest in society bearing the biggest burden, making it a key health inequalities issue (figure 4). The importance of cofactors, including genetic inheritance[22] and environmental factors, is not sufficiently recognised, including the frequent interaction of obesity and viral hepatitis with excess alcohol consumption leading to more severe liver disease and development of primary hepatocellular carcinoma (HCC).

As a result of increasing rates of obesity, 25% of the population are estimated to have non-alcoholic fatty liver disease; about 10% of these people have been diagnosed in community studies to have evidence of advanced liver fibrosis. Progression to end-stage liver disease and primary hepatocellular carcinoma is increasingly reported.[23] Development of type 2 diabetes, which is increasing in frequency in parallel with obesity, carries an additional risk factor for liver disease, namely non-alcoholic fatty liver disease. According to Duncan Selbie, Head of Public Health England, the obesity crisis could result in the number of people with type 2 diabetes trebling during the next 20 years to 6·2 million by 2034.

With respect to treatment for chronic viral hepatitis, substantial grounds exist for optimism, even to the extent of being able to contemplate eradication of both hepatitis B and C within two to three decades. Drugs for the treatment of chronic hepatitis B infection have improved so that treatment is nearly 100% effective in controlling progression of liver disease.[24] New drugs being introduced for hepatitis C infection are revolutionary because they are more effective in viral clearance, need shorter periods of treatment, and have fewer side-effects than do previous drug treatments. Associated financial costs will be high in the short term,

but ultimately will be cost effective and easy to justify to medium-term health-care strategists.[25] Barriers to progress include the unrecognised substantial pools of people infected with hepatitis C or hepatitis B in the community and the underutilisation of vaccines against hepatitis B. The pools of infection are being added to each year by the input of immigrants coming from countries with a high prevalence of viral hepatitis. Projections show that the frequency of end-stage liver disease from hepatitis C infection will increase until 2020, and that the recorded increase in frequency of HCC is the result of a complication of cirrhosis from all causes (2–4% every year).[26]

Although the emphasis throughout the report is on the major preventable causes of liver disease, attention needs to be paid to the less common liver disorders such as autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and drug-induced liver injury. The formation of National Consortia, which bring together clinical experience, data, and research programmes from several liver centres, is a welcome development. New designer therapeutic molecules based on a better understanding of disease pathogenesis offer substantial hope for the future. However, as with the lifestyle disorders, early diagnosis is essential if disease progression is to be reduced in these disorders. This early detection is dependent on increased awareness of these uncommon disorders in general practice so that early referral can be made for specialist care.

Paediatric liver disease encompasses a range of common and uncommon disorders, but overall has been a success story. Centralisation since 1999 of specialist services for paediatric liver disease to three national centres, allows children with serious neonatal liver disease to survive with a good quality of life into adolescence, although safe transition for these children to adult care is still problematic. Of increasing concern is the number of young people who are drinking to excess from an increasingly early age. Young people who misuse alcohol tend to be seen by general practitioners (GPs) or accident and emergency doctors who underestimate the risk of liver injury at such an early age and subsequently the liver disease goes undetected until adulthood.

A major difficulty is the often silent nature of chronic liver disease. Most patients present late at the stage of cirrhosis and usually to hospital services with bleeding varices, ascites, or encephalopathy, by which time a substantial mortality and morbidity is probable.[27] Findings of a UK population-based study[28] of more than 5000 people with cirrhosis showed 1 year and 5 year survival rates of 0·84 and 0·66, respectively, for outpatients, but only 0·55 and 0·31 for patients admitted to hospital. Although the lag time between ongoing liver injury to the development of cirrhosis provides opportunities to intervene, half of patients with alcohol-related cirrhosis who become abstinent still die before their liver recovers.[29] Similarly, many cases of chronic viral hepatitis B, viral hepatitis C, and obesity-induced liver disease go undetected until first presentation with complications of cirrhosis or a primary HCC. Liver disease arises in identifiable high-risk patient groups, but there is no national policy or widely accepted method for screening programmes, despite the availability of several excellent techniques. Furthermore, knowledge and awareness of liver disease in primary care and community care is low compared with other substantial causes of premature mortality, such as cardiovascular disease.

Mismanagement of complications of cirrhosis (eg, ascites, variceal bleeding, renal dysfunction, and sepsis) were key recurring themes in the 2013 NCEPOD report[2] on the unacceptably high mortality and poor standard of care in hospital admissions for alcohol-related cirrhosis. The NCEPOD report[2] emphasised unacceptably slow access to endoscopic intervention after acute variceal bleeding, along with insufficient specialist expertise by inadequate numbers of trained hepatologists. Only 3% of patients who are ill with liver issues and other illnesses were seen on admission to hospital by a consultant hepatologist, with a further 17% seen by a gastroenterologist, and most were looked after by general physicians and doctors of other specialties. Dedicated hepatology wards were available in only 43 (21%) of 203 hospitals and 45 acute hospitals had no hepatology expertise or no formal arrangements to transfer patients to a liver centre. Only 23% of hospitals had a multidisciplinary alcohol care team despite the joint 2010 British Society of Gastroenterology (BSG)/British Association for the Study of the Liver (BASL)/Alcohol Health Alliance recommendations, NHS evidence, and NICE evidence-based recommendations stating that each acute hospital should establish at least one team that could be integrated in primary and secondary care. The report[2] called for all patients with decompensated cirrhosis to be seen by a consultant gastroenterologist or hepatologist ideally within 24 h of admission to hospital and no longer than 72 h.

Postcode lottery of specialist services and centres

In-hospital mortality rates for cirrhosis and liver failure vary across the country, with some acute trusts consistently reporting mortality rates of more than double those of the better centres (figure 5). The All Party Parliamentary Hepatology Group (APPHG) noted "grave concerns about patchy service provision across the country, the late diagnosis of patients and a lack of the necessary central drive and prioritisation".[3] There was concern and disappointment that despite the commitment embodied in the NHS reforms to improve the health of the poorest, fastest, rates of liver disease continue to increase and it was concluded that "extensive and coordinated national action is urgently required". At

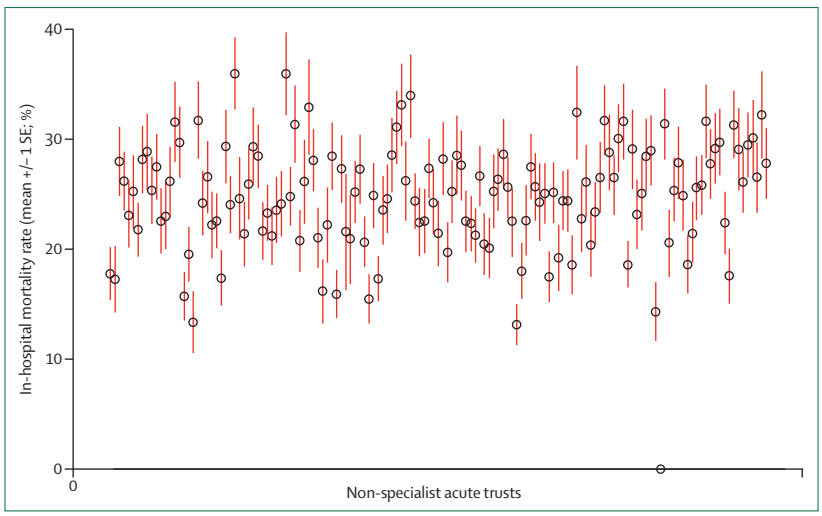

Figure 5: **Liver disease or cirrhosis in non-specialist trusts in England, 2003–13**
Data for non-elective liver admissions, including International Classification of Disease (ICD) codes, were extracted from the Dr Foster website, and re-coded according to cirrhosis or liver failure and other liver disease codes. Parts of inpatient care were calculated by year of admission using Statistical Package for the Social Sciences, mean (standard error). In-hospital mortality rates are plotted for all sites categorised by hospital trust for an ICD-10 code for liver cirrhosis or failure (Dr Foster Limited, personal communication). SE=standard error. Unpublished analysis of Dr Foster data, May 2014, Nick Sheron.

For the **Dr Foster website** see https//my.drfoster.uk

present, service provision and clinical need are disjointed. The benefits of improved provision of hospital liver care in the reduction of premature mortality rates exceed those of almost every other major disease, especially when the causes of liver disease are preventable.

Imbalances between the present service needs and disease burden are emphasised by the distribution of liver transplant services—accidents of history rather than thoughtful planning. England has six transplant units: in Birmingham, Leeds, Cambridge, Newcastle and two in London. Rates of transplantation tend to be associated with local transplant services—eg, the west Midlands (15·7 per million population [pmp]) has the highest per person transplant rate, whereas densely populated areas such as the northwest (10·6 pmp) and south-central (9·8 pmp) have the lowest rates of transplantations despite some of these regions having high burdens of disease (figure 6). Large conurbations are devoid of regional transplant services and the wide associated benefits of skills in hepatocellular carcinoma, acute liver failure, and hepatopancreatobiliary surgery. Liver transplant rates for the UK population are about half of those of other European countries. Failure to develop services for liver transplants during the past two decades has left the service in a poor position to adapt to growth and the increasing number of donor organs becoming available for transplantation, the result of the government's strategy.[30]

Similarly, the distribution of other specialist liver services was not planned in accordance with the needs of the local population or the prevalence of liver disease. To different extents these centres have the ability to do specialist liver work, including liver resections, transjugular intrahepatic portosystemic shunt (TIPSS) procedures for portal hypertension, tumour ablation for liver cancers, and to investigate complex liver disorders, with their dedicated liver intensive care and high quality laboratory facilities. However, no formal categorisation of specialist liver centres has been done and the network relationships between specialist centres and surrounding district hospital services are haphazard.

Deficiencies in consultant care

Most liver services in the UK are provided by gastroenterologists who might have had as little as 6 months training in liver disease, and by general physicians who have had no specialised liver training. This situation shows a historical lack of priority accorded to liver disease in the training of gastroenterologists and a continuing failure to formalise the training of hepatologists. The most recent survey of adult liver services was the 2010 Department of Health's Census of Medical Workforce,[31] in which information was obtained from 878 of 904 gastroenterology or hepatology consultants in 124 of 149 trusts. Only 122 (14%) consultants spent more than half their time treating patients with liver disease, an additional 206 (23%) were categorised as gastroenterologists with some interest in liver disease, and 551 (63%) were purely luminal gastroenterologists. Hepatologists were located mainly in transplant (40%) and specialist referral centres (30%), with only a few in the 19 other hospitals surveyed. Almost three-quarters of district general hospitals (73%) had no dedicated hepatology services. Yet acute admissions with life-threatening liver disease are on a par with myocardial infarction and stroke in the need for urgent treatment measures.

Evidence has shown that patients with liver disease are subject to discrimination as a result of the continuing stigma associated with the disease; many hepatologists will have experienced this when admitting these patients to an intensive care unit; when alcohol is involved, a moral question of whether intensive care is justified is often asked. Liver diseases and particularly alcohol-related liver disease, seem to be viewed as self-inflicted illnesses in a way that obstructive airways disease, ischaemic heart disease (both tobacco related), or type 2 diabetes (obesity related) are not. Of 195 Quality Improvement Indicators set by NHS England, 41 are for heart disease, 24 for diabetes, 23 for cancer, but not one is for liver disease. The only indicator to mention alcohol is MH 11, "alcohol consumption by patients with schizophrenia".[32]

In this Commission we include strategies with details on how to reduce premature mortality from liver disease by setting out a proposal for hospital services for the early detection of disease in primary care and, most importantly, for tackling the underlying lifestyle risks. If all the recommended steps are implemented, many of which need additional governmental regulatory action, liver mortality rates will decrease,

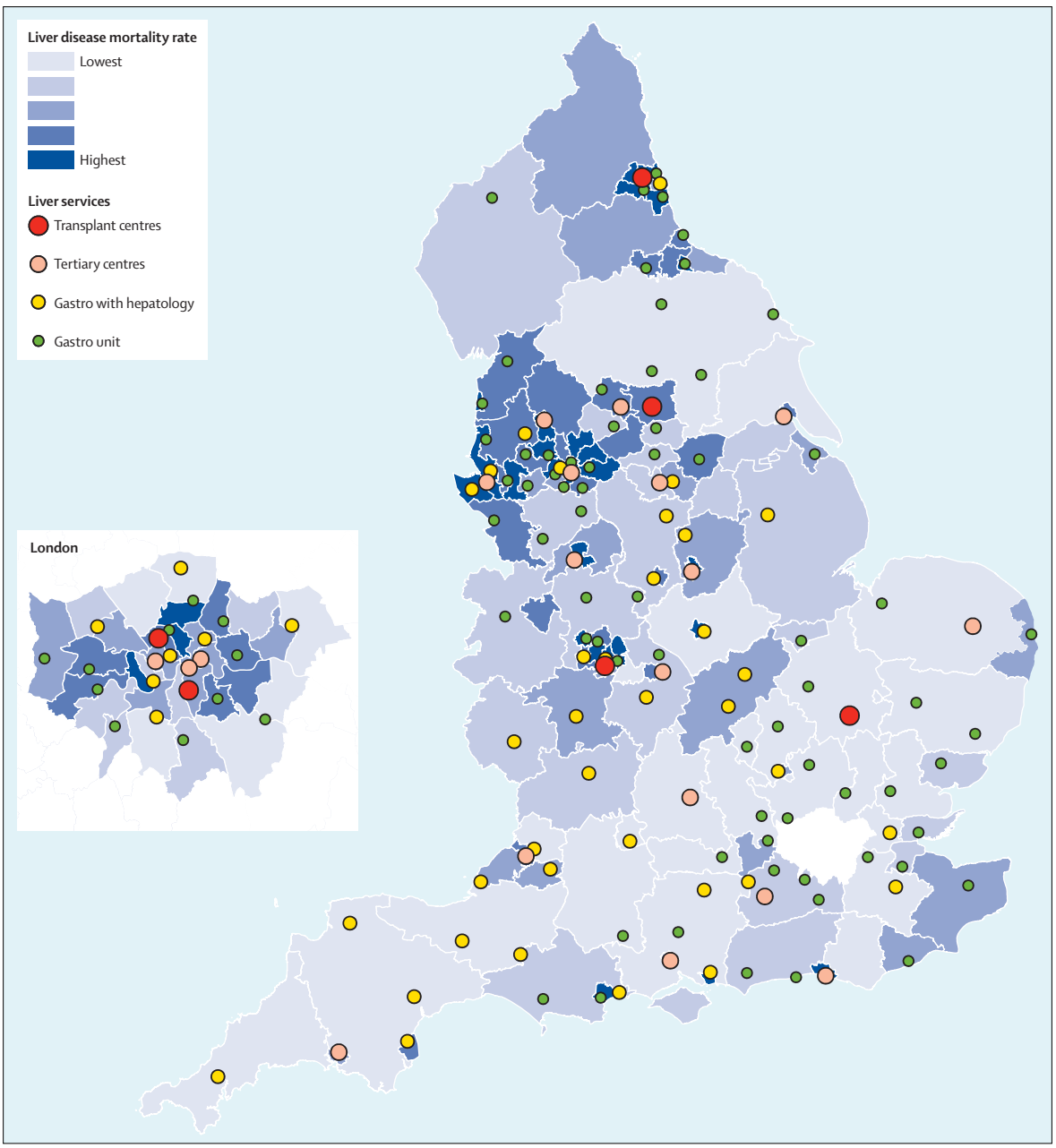

Figure 6: **Distribution of liver services in England in relation to mortality of chronic liver disease, 2006–07**
Mortality rates per 100 000 population. Figure reproduced from National Health Service Right Care Atlas of Variation,[7] by permission of Right Care.

with profound benefits to health and social wellbeing, economic productivity, and a reduction in costs to health services.

How to improve hospital care and reduce premature mortality

The high mortality rates from cirrhosis and the inadequate care provided in hospitals for patients dying from alcohol-related diseases, graphically show the deficiencies in the present provision of hospital liver services in England. These deficiencies could be assumed to apply to the full range of causes of chronic liver disease in patients admitted to hospital. In the NCEPOD analysis,[2] 73% of patients who died from chronic liver disease had been admitted via the emergency department, and only 17·6% via the GPs. Findings of another study[33] of patients dying from liver disease showed that 92% died in hospital, adding to the impression that community support at every stage of liver disease, from early diagnosis to palliative care, is

Panel 1: **Portsmouth district liver service**

Staff at this hospital include:

- Three consultant hepatologists
- Four hepatology nurse specialists
- Hepatitis B and hepatitis C services, including outreach clinics
- Five alcohol specialist nurses, delivering a service available 7 days a week
- Transient liver elastography facility
- Dedicated endoscopy lists for varices
- 24 h, 7 days a week out-of-hours gastrointestinal bleeding rota with gastroenterologists
- Critical care with a liver multidisciplinary team
- Six consultant-led dedicated liver clinics per week
- Initial assessment for transplantation (with The Royal Free Hospital, London, UK)

underdeveloped, compounding the shortcomings of the hospital services. In view of the long interval (often decades) between early disease to death, care should be given in the primary care setting and hospital services should provide high quality and protocolised support for episodes of acute deterioration that are characteristic of the late stages of cirrhosis.

We aim to address service delivery for liver disease in the hospital setting, including consideration of whether services are appropriately sited and resourced. We will state the case for the appointment of more accredited hepatologists and liver specialist nurses in acute service provision based in district general hospitals, aligned with improved access to specialist liver centres for more complex care.

Proposal for hospital services

Improved care for the treatment of cirrhosis complications, including use of renal support, improved endoscopic management of variceal haemorrhage, and advanced techniques (eg, Transjugular Intrahepatic Porto-Systemic Shunt [TIPSS]), are all essential in the reduction of in-hospital mortality rates for cirrhosis failure. To achieve this reduction, liver care in hospitals should be accredited at two levels—acute district hospital services (so-called liver units) and specialist regional centres—to allow bidirectional transfer of patients between these two levels of care on the basis of clinical need.

Acute liver services as part of gastroenterology and liver units in district general hospitals

District general hospitals typically serve a population of around 250 000. Patients who are acutely ill with liver disease are admitted to these hospitals where care is expected to be competent and effective in stabilising the patient by managing the main triggers of liver decompensation in cirrhosis and, when appropriate, escalating care to regional centres. The important complication of variceal bleeding would be managed in accordance with clearly stated standards for intervention and outcome, in a protocol with comparable visibility and commitment as that for acute stroke and myocardial infarction. District hospitals would also be expected to competently manage infection in patients with cirrhosis, which is often the trigger of hepatic decompensation and early renal dysfunction.

For adequate delivery of this service, a team of at least six consultants will be needed, consisting of at least two consultants in hepatology with 2 years of training in complex hepatology and with two of the other four being consultants in gastroenterology and hepatology who have at least 1 year of training in complex hepatology. All gastroenterologists in the team should be competent in the endoscopic management of bleeding varices. This configuration could deliver the important metrics of endoscopic intervention within 24 h of admission to hospital, as recommended in the British Society of Gastroenterology guidelines,[34] and a review of the patient's clinical hepatology also within 24 h after admission. The range of services provided in any one centre will depend to some extent on the size of population served, but care for viral hepatitis, imaging surveillance for HCC, and preliminary assessment for liver transplantation should all be within the remit of these units.

The availability of skills in histopathology is essential to such a service for both diagnosis and assessment of therapeutic response in patients. This can be either on-site or through a regional network arrangement. Liver biopsy is a gold standard test in many liver disorders, particularly viral hepatitis and non-alcoholic steatohepatitis (NASH), and in the less common disorders referred to, such as primary biliary cirrhosis, autoimmune hepatitis, and drug-induced liver injury. The importance of this test as a component in hepatology practice cannot be over emphasised. Similarly, skills in the radiology department are essential both in the imaging procedures of CT and MRI and particularly in ultrasound examination, which is widely used and necessary for the screening of liver disease.

Portsmouth has a good example of a district liver service. The service was developed in 4 years, with the initial appointment of a single-handed hepatologist, and has now expanded (panel 1). Although district general hospital liver units of this size have the facilities to provide some aspects of specialist care, restrictions will need to be agreed to ensure appropriate onward referral for more highly specialised or complex services, including the treatment of hepatocellular carcinoma. An important recommendation of the Commission that needs to be taken forward for implementation, is the drawing up of an overall plan for the country that shows the links between district general hospital liver units and the specialist centres.

Other district hospitals that provide a wide range of hepatology services include Frimley Park in Surrey, Bournemouth, Exeter, Brighton, Norwich, and Derby.

The idea of having a so-called "liver champion" in every district general hospital is part of the recommendation for improving acute hospital provision and to help with the development of defined clinical pathways and care bundles, many of which would be designed with colleagues in acute medicine and critical care. This champion would liaise closely with external stakeholders such as public health, primary care, and community services. Liver diseases disproportionately affect the socioeconomically deprived and patients often enter a care pathway remote from the service they need and often remain invisible to that service, a scenario that could be difficult to sort out. The Champion would also have to ensure all facilities and skilled personnel were available in the hospital for assessing and stabilising patients who are seriously ill before involving the regional specialist centre.

Specialist regional centres at university hospitals

About 1–2 million people are served by specialist regional centres at university hospitals, the defining characteristic of which is the ability to deliver elements of specialist care possibly in isolation, but more typically in a portfolio of services. Traditional service areas are complex medical hepatology, HCC, hepatobiliary surgery, and liver transplantation (incorporating the management of acute liver failure). The management of hepatitis C, with the new, more effective, but very costly direct acting antiviral drugs, can now be added to this list, based on the 16 centres that have been commissioned by The Department of Health this year to deliver a rapid early access programme for these drugs. Specialist centres will also have expertise in allied disciplines including interventional radiology, virology, and liver histopathology. The liver service at St George's Hospital in London, UK, is an example of a non-transplant specialist centre (panel 2)

Well defined indicators can be specified for involvement of a specialist centre, for example re-bleeding from varices within 7 days of the index bleed in the liver unit of district general hospitals. Such metrics are amenable to audit and quality assessments and at the specialist centre, the quality of the TIPSS service is another metric. At present, TIPSS provision is haphazard because availability does not map the frequency of cirrhosis and portal hypertension in the country. The present situation whereby patients who are critically ill often wait for several days for an inter-ITU transfer to a distant TIPSS centre, is unacceptable. More TIPSS facilities need to be established in specialist centres through close collaboration between interventional radiologists, with the setting up of emergency interventional or vascular radiology rotas. The Royal Free Hospital in London, UK, is an example of best practice with respect to TIPSS, and the hospital has at times offered an outreach component to its service. Provision of interventional radiology services at the specialist centres, including ablation techniques for HCC, will need to be developed in collaboration with the Invasive Radiology Clinical Reference Group and their recommendations on vascular centres. Other clinical triggers for referral to a specialist centre would include the development of hepatorenal syndrome, intractable ascites, and difficult to control hepatic encephalopathy. Optimum management of these disorders will need predictable access to renal replacement and critical care facilities. Alignment of some of the hepatology aspirations with those of the clinical research outsourcing (CRO) facilities for hepatobiliary surgery would be worthwhile, especially because an additional 222 consultants and intensivists are estimated to be needed to achieve sustainable on-call rotas.[35]

Management of HCC is an example of specialist care that could be delivered partly in one specialist centre in collaboration with another centre undertaking liver transplantation. All cases that might benefit from liver transplantation should be discussed at least once in a multidisciplinary meeting held by the transplant centre. Thereafter, surgical resection or locoregional treatment could arguably be effectively delivered in a non-transplant specialist centre; however, the increasing complexity of the options for locoregional intervention after chemo-embolisation and radio-frequency ablation might constitute a rationale for centralisation of these services. Consultant hepatology input should be in first place throughout the care pathway for a patient with HCC, liaising with oncology as needed at specific stages. The HCC service should have appropriate links with palliative care and end-of-life services that extend into community care.

Figure 6 shows the distribution of the recognised specialist services in relation to the variability in mortality due to chronic liver disease in people aged 75 years and younger.[7] On the basis of a catchment population of around 2 million for each specialist service centre, an estimated 30 specialist centres are needed. Each centre would have at least six consultant hepatologists (the minimum number needed to deliver a

***Panel 2*: St George's specialist liver centre (London, UK)**

Staff at this hospital include

- Three and a half full-time equivalent consultant hepatologists with a dedicated junior team
- Transjugular intrahepatic porto-systemic shunt service
- Locoregional therapy for treatment of hepatocellular carcinoma (including transarterial chemoembolisation and radio frequency ablation)
- Commissioned centre for hepatitis C virus early access programme
- Joint appointment with King's Liver Unit (London, UK) to facilitate liver transplant pathway

	Transplant operation available	Tertiary HPB unit	HCV treatment led centres
Northeast			
The Freeman Hospital, Newcastle	✓	✓	✓
Northwest			
Manchester Royal Infirmary	..	✓	✓*
North Manchester General Hospital	..	..	✓*
Royal Liverpool University Hospital	..	✓	✓
Aintree University Hospital, Liverpool	..	✓	..
Yorkshire			
St James University Hospital, Leeds	✓	✓	✓
Sheffield Teaching Hospital	..	✓	..
West Midlands			
Queen Elizabeth Hospital, Birmingham	✓	✓	✓
University Hospital of North Staffordshire	..	✓	..
East Midlands			
Queens Medical Centre, Nottingham University Hospital	..	✓	✓
University Hospital Leicester	..	✓	..
East of England			
Addenbrookes Hospital, Cambridge	✓	✓	✓
London			
Hammersmith Hospital, London	..	✓	✓†
Chelsea and Westminster Hospital, London	..	✓	✓†
Royal Marsden Hospital, London	..	✓	..
Royal Free Hospital, London	✓	✓	✓
Barts and The London Hospital	..	✓	✓
King's College Hospital, London	✓	✓	✓‡
St George's Hospital, Tooting	..	..	✓‡
Guys and St Thomas's Hospital, London	..	✓	..
Southeast			
John Radcliffe Hospital, Oxford	..	✓	✓
Southampton University Hospital	..	✓	✓
The Royal Surrey County Hospital	..	✓	✓
Basingstoke and North Hampshire Hospital	..	✓	..
Brighton and Sussex University Hospital	..	..	✓
Southwest			
Plymouth Hospital	..	✓	✓
University Hospital, Bristol	..	✓	✓

A basis for the estimated 30 needed specialist centres. HPB=hepatopancreatobiliary. HCV=hepatitis C virus. *Joint programme. †Joint programme. ‡Joint programme.

Table 1: **Geographical location of hospital or trust transplant centres, tertiary hepatopancreatobiliary surgical units, and the hepatitis C virus treatment-led centres**

service available 24 h a day for 7 days a week), possibly with a profile of subspecialisation. Present provision falls substantially short of this target and in the 2010 census,[31] only 17 centres had three or more hepatologists, of which six were transplant units. The network of centres undertaking hepatobiliary surgery and complex liver care being developed for specialised commissioning by NHS England could be a valuable resource in terms of numbers of staff and skills to support development of the service. A substantial range in the level of services provided in the specialist centres and the hepatitis C virus centres recognised in 2014, which will provide rapid access treatment facilities for the new high cost drugs. At present some of the recognised hepatobiliary surgical units only do pancreatic surgery, whereas others deal mainly with hepatic resections for colorectal metastases. Standardisation of the range of surgical services and promotion of colocalisation with expertise in medical hepatology are credible development strategies. 27 centres in England would fulfil part or all of the requirements for a specialist centre (table 1).

The recommended expansion of specialist centres also has to address imbalances in service provision relating to geography and disease burden (figure 6). Access to and interaction with specialised services could be improved through improved outreach—ie, clinical links to liver units at district general hospitals. Several UK liver transplant centres offer some outreach or satellite clinics to associated hospitals. The extent of involvement varies, but some activity, such as pretransplant assessment tests, can be devolved to the local district general hospital. A 2013 review[36] identified key issues when setting up satellite arrangements, including a critical mass of referrals, managerial engagement from both partner organisations, and the crucial issue of patient involvement. For patient involvement, heterogeneity of patients needs to be recognised because some might prefer local follow-up after transplantation whereas others might choose to return to the specialist centre. Derriford Hospital in Plymouth, UK, is an example of where this care arrangement has been developed to a high level of sophistication in association with King's College Hospital (London, UK).[36]

Liver critical care for acutely ill patients

Deficiencies in access to critical care for patients with liver disease need to be corrected as part of the development of better liver units in district general hospitals. Although critical care should be well established in the specialist centres, patients with liver disease who are acutely ill need to have proportionate access to high dependency facilities in the initial district general hospital to which they are referred to. This is evident simply from the number of patients involved, with 3000 admissions recorded for variceal bleeding every year.[37] Previously, provision of liver critical care in district general hospitals was difficult because of the sense of futility and the stigma associated with self-inflicted illness, especially alcohol and recreational drug misuse. Both the paucity and the potential value of critical care were shown in an analysis of 31 912 admissions to ITU between 1996 and 2012. The percentage of patients with cirrhosis increased from a mere 1% to 3% by the end of the study in 2012, whereas the survival rate increased from 40% to 55% overall for patients admitted and from 40% to 60% in patients with alcohol-related cirrhosis.[38] The Intensive Care National Audit and Research Centre (ICNARC) database shows more than

100 critical care units admit patients with cirrhosis, but how many of these have the necessary associated expertise in medical hepatology is unclear.[39]

Specialist centres have a pivotal role in defining the standards and expectations for intensive care provision at the level of district liver services. The liver intensive care unit at King's College Hospital (London, UK) is an example of best practice. The initial objective of this facility when set up in 1973 was to improve the care of patients with acute liver failure. A review[38] of 3300 patients treated at this hospital confirmed the success of this approach with most patients now surviving this illness. In 48 years, the liver unit has expanded from the initial two beds to 15 beds and extended its work into the management of acute and chronic liver failure and post-surgical liver care.

Liver transplant services

Liver transplantation has tended to be seen as defining the highest level of sophistication in liver services in the UK, because the personnel and expertise involved have raised the standard of other associated services, such as hepatobiliary surgery, critical care, and interventional radiology. By international standards, mortality on the waiting-list for liver transplantation in the UK is quite low and outcome data are excellent in all six of the English liver units. However, there are substantial differences in size of centres and waiting times between centres, and a variation in cost of more than 50% between the lowest and highest cost centres. Perhaps the biggest concern is that the number of centres that do liver transplantation has not changed for more than 20 years and an imbalance exists between geographical configuration and patient need. Also of concern is whether there is sufficient capacity to respond to the T2020 strategy,[30] which is on target to increase the number of liver transplants by at least 50% by the year 2020. A firm recommendation of our Commission is that now is the time for a major review of provision for liver transplant services in England. This review should have regard to provision of additional centres for areas with large populations, such as the northwest and south-central, which have the lowest rates for patient transplants.

Visibility and functioning of hospital network arrangements

All units, whether district general hospital liver units or specialist centres, should be accredited to provide an explicit range of services, including transfer and network arrangements. Appropriate endoscopic management of a variceal bleed within 12 h of admission to hospital will ultimately not be successful if it takes 5 days to transfer the patient to a specialist centre for a TIPSS after a re-bleed. Similarly, a patient developing hepatorenal failure successfully resuscitated on initial admission to the district general hospital's liver unit, has to have timely access to the specialist centre for renal replacement therapy. Obstructions or delays in the service will need to be managed between district general hospital liver units and the specialist centres, driven by clinical need. Additionally, arrangements for the provision of services outside the hospital or centre units' respective portfolios will also need to be formalised. Specialist centres will be assessed on the basis of their ability to accept referrals within timeframes appropriate to the indication for referral. In turn, the referring centres will need to become adept at quickly accepting the return of these patients for continued local care. This fluidity in patient care will ultimately affect the success, or otherwise, of the network relationship.

Methods to help with changes: care bundles, chronic disease management, and operational delivery networks

The introduction and value of goal-directed so-called care bundles for the early management of medical emergencies is shown by the successful Surviving Sepsis campaign.[40] Inevitably, a balance is needed between protocolised and personalised medicine.[41] Care bundles for decompensated cirrhosis could help substantially in setting of standards and one such model is being piloted in Newcastle Hospitals Trust, UK. For the longer term management of cirrhosis, implementation of a model for chronic disease management (CDM) is recommended to increase integration with multidisciplinary services in primary care, district hospital liver units and specialist centres. In view of the high number of index admissions, frequent unplanned readmissions, prolonged hospital stays, and high mortality of patients with cirrhosis, much can be gained from such an approach. Successful programmes of CDM have coordination of care, designs for delivery systems, clinical guidelines, information systems support for patient self-management, and effective community services.[42] In an Italian study,[43] use of a structured CDM model for patients discharged from hospital with cirrhotic ascites showed significantly reduced 30-day readmissions (from 42% to 15%), 12-month readmissions (71% to 46%) and 12-month mortality (46% to 23%) and achieved a 46% reduction in health-care costs. Many basic mechanisms needed to deliver CDM programmes for chronic liver disease both at the level of district general hospitals and specialist centres are already in place, but their integration in a CDM model needs to be further addressed. The model for an Operational Delivery Network (ODN) outlined in the *NHS England Strategy for Operational Delivery Networks* could be appropriate in specific settings of district general hospitals. This model allows local centres to work together by pooling expertise and sharing standard operating procedures and outcome data. An advantage of this system is the local ownership of services, while benefiting from the wider collective expertise of the network.

For more on the **Liver Network model pilot in Newcastle Hospitals Trust** see http://www.nescn.nhs.uk/group/Liver/

Panel 3: **Acute hospital model for an alcohol care team**

- A consultant-led, multidisciplinary, patient-centred alcohol care team to be integrated across primary and secondary care
- 7 day alcohol specialist nurse service
- Coordinated policies for the emergency department and acute medical units
- Rapid assessment, interface, and discharge liaison psychiatry service
- An alcohol assertive outreach team for frequent attenders to hospital
- Formal links with local authority, clinical commissioning groups, public health, and other stakeholders

Care for alcohol misuse in the hospital setting

Detailed evidence-based recommendations for models of multidisciplinary alcohol care in acute hospitals have been drafted by the BSG, the Alcohol Health Alliance UK, and the BASL,[44] along with those of the Quality, Innovation, Productivity, and Prevention (QIPP) case study,[45] and the Health First strategy.[46]

An essential requirement for each district general hospital liver unit and specialist centre is the establishment of a multidisciplinary, consultant-led alcohol care team, which is integrated across primary and secondary care (panel 3). Lead consultants need to have designated sessions and sufficient time to collaborate with public health (local authority), primary care organisations, patient groups, and other key stakeholders to develop and implement district strategies for alcohol through integrated treatment pathways.

A 7 day alcohol specialist nurse service is an essential component of this model team, together with a skill mixture of liver specialist and psychiatry liaison nurses, who would provide comprehensive assessments of physical and mental health, brief interventions, and access to services within 24 h of admission to hospital. A specialist nurse-based alcohol service in Nottingham reduced admissions for detoxification by 66%, clinical incidents by 75%, γ-glutamyltransferase concentrations by 50%, and day occupancy of beds in patients with cirrhosis by 50%.[47] The hospital alcohol care teams should coordinate policies of care across acute departments, including accident and emergency and acute medical units. In combination with the ward-based National Early Warning Score, launched by the Royal College of Physicians,[48] the alcohol specialist nurses will be able to drive through an appropriate escalation of care for individual patients. Linkage through alcohol assertive outreach teams with active community case management is necessary to deal with the patients having frequent attendances and admissions to hospital due to alcohol misuse.[49] Large savings from avoided admissions and reduced NHS costs have been reported from UK hospitals in Bolton, Salford, Nottingham, and Portsmouth.[45] Input from addiction psychiatrists together with liaison psychiatrists is also needed. The Birmingham Rapid Assessment, Interface and Discharge (RAID) model of liaison psychiatry, which links patients to the appropriate care pathway in the community, has led to major savings in costs and use of hospital beds.[45]

Additional training for consultant hepatologists and liver specialist nurses

Expansion in the number of consultant hepatologists and consultant gastroenterologists who have experience in hepatology to provide the envisaged improvements in hospital care will have to be underpinned by substantial changes in the training model. Consultant hepatologists would have an initial 3 years of general gastroenterology training, followed by a final 2 years dedicated to hepatology training, whereas consultant gastroenterologists with experience in hepatology would have 1 year of liver training in the final 2 years of the specialty programme. As defined in the 2010 gastroenterology curriculum, so-called core hepatology training in a liver centre needs to increase from the present 6 months to 1 year.[50] Initially, the aim would be for a minimum of 40% of trainees to be competent in hepatology at the end of their training, with the figure increasing to 100% during the next 5 years. Although 1 year hepatology fellowships for trainees wanting specialist accreditation in hepatology were created in 2004, too few were trained (16 trainees [2%] of the national pool) and difficulty was encountered in recruiting to these positions. Findings of a survey[51] of gastroenterology and hepatology trainees showed that 25% of trainees in their fifth year or longer in training had not spent any part of their training in a recognised liver unit, or those with some experience had spent a median time of only 7·8 months. A third of trainees believed that their rotations were inadequate to deliver competent care in hepatology and 20% felt unable to confidently manage patients with liver disease.[52] Commitment to improve hepatology training is mandatory for the successful implementation of proposals outlined in this Commission that aim to improve hospital care and reduce premature mortality.

Substantial investment will be needed to increase the numbers of specialist liver nurses who play a pivotal part in the overall care of patients with liver disease, and bridge the gaps between clinicians and families or carers and between primary and hospital care. Benchmarked standards for different roles in nursing will need to be developed for skills, knowledge, and competencies. The Royal College of Nursing publication will help with this.[53] At present, nurse specialists are involved to a major extent in treatment of viral hepatitis and in care for various other hepatology disorders, often within nurse-led outpatient clinics. To maximise their contribution, the role of a lead hepatology nurse should, as recommended, be promoted. This would be an advanced nurse practitioner or nurse

consultant who would have responsibility for at least one or two additional hepatology specialist nurses, specialising in specific disease areas (eg, chronic hepatitis C, alcohol, hepatocellular carcinoma, and palliative care). Liver transplant centres have formalised nursing input through their teams of recipient coordinators and their role in longitudinal care could be expanded like in the USA. Finally, every hospital department needs to be encouraged to provide link nurses to attend regular meetings with the trust liver specialist nursing team for education and service development issues. This additional training for nurses will help with close working with relevant nursing partners in the hospital—eg, those associated with emergency admissions, orthopaedics, and cardiology services. All these points will help to improve hospital care for liver disease (panel 4).

***Panel 4*: Key recommendations to improve hospital care**

1. Liver care in hospitals should be accredited at two levels—acute district general hospital liver units and regional specialist centres—with facilities for the rapid, appropriate, bi-directional transfer of patients, and with defined network arrangements, including primary care, to deliver comprehensive multidisciplinary care
2. Liver units in acute district hospitals that typically serve a population of 250 000 would have at least two consultant hepatologists and four consultant gastroenterologists, a minimum of two of these would have hepatology experience, to be able to provide acute services 7 days a week for the emergency care of patients with decompensated cirrhosis, gastrointestinal bleeding from oesophageal varices, and acute alcoholic hepatitis
3. Regional specialist centres, serving a population of 1–3 million and staffed by at least six consultant hepatologists, would be responsible for the delivery of specialist care including high level critical care, treatment of hepatocellular cancer, high cost services for viral hepatitis, hepatopancreatobiliary surgery, and liver transplantation in some centres
4. A national review of liver transplant units should be commissioned to establish the need for additional centres in the northwest and southwest regions of the UK and to ensure adequate capacity for use of the increasing number of donated organs
5. Every acute hospital should establish a consultant-led, multidisciplinary, patient-centred alcohol care team, which would be integrated across primary and secondary care and comprise of a 7 day alcohol specialist nurse, liaison psychiatry, and outreach teams
6. Goal-directed so-called care bundles for the early management of cirrhosis and its complications should be the normal treatment in every hospital and should be made a local commissioning for quality and innovation payment
7. Training for so-called core hepatology should be formalised with the final year of specialist training for district hospital consultants and a final 2 years for specialist centre consultants (figure 6)

Strategies and specific measures to address lifestyle risk factors of liver disease

Obesity and non-alcoholic fatty liver disease

Understanding of non-alcoholic fatty liver disease is still at an early stage and has only started to gain broad professional recognition. Furthermore, only a small proportion of the general public know that being overweight or obese increases the risk of developing liver disease, and that there is much to learn about the natural history and effective treatments for this disease. Nevertheless, much can be done to minimise the resulting effects of fatty liver disease, taking into account the extent of the present burden in the UK and knowledge of its natural history.

Almost a quarter of the UK population are obese and obesity levels are rising, leading to a potential disaster for the NHS because when these individuals age they will have an increased rate of type 2 diabetes, heart disease, and cancer. In addition to these well publicised health harms, obesity and diabetes are also associated with fatty infiltration of the liver, termed non-alcoholic fatty liver disease. A third of obese individuals have this disease, and in almost one in ten, it can result, during 20–50 years, in an inexorable process of silent liver scarring leading to cirrhosis, liver failure, primary hepatocellular carcinoma, and death.

Assuming that 23% of the population is currently obese, the overall prevalence of non-alcoholic fatty liver disease in the country is between 17% and 33%.[53–55] Moreover, although people who are obese with a high body-mass index (BMI; ≥30 kg/m^2) are much more likely to develop non-alcoholic fatty liver disease, this disease can also be found in people with a healthy BMI (18·5 to 24·9 kg/m^2), with the best studies reporting a prevalence of 16–20% in individuals of a healthy weight.[54,56] This discrepancy emphasises one of the limitations of the use of BMI as a surrogate marker of obesity when it is the distribution of body fat—notably central (abdominal) obesity not total fat or BMI—that is more strongly associated with non-alcoholic fatty liver disease and other metabolic sequelae.[57] A more accurate method for the assessment of fat distribution, particularly central obesity, is through the measurement of waist circumference taken at midway between the lowest rib and the iliac crest (>94 cm for men and >78 cm for women) with different cutoffs according to sex and ethnic origin.

Obesity levels in children have risen steeply during the past 10 years. In state school children in England, annual measurements of height and weight show a present prevalence of obesity of 9·3% in reception classes (age 4–5 years) and 18·9% in year 6 children (age 10–11 years). This is an approximate doubling in prevalence between

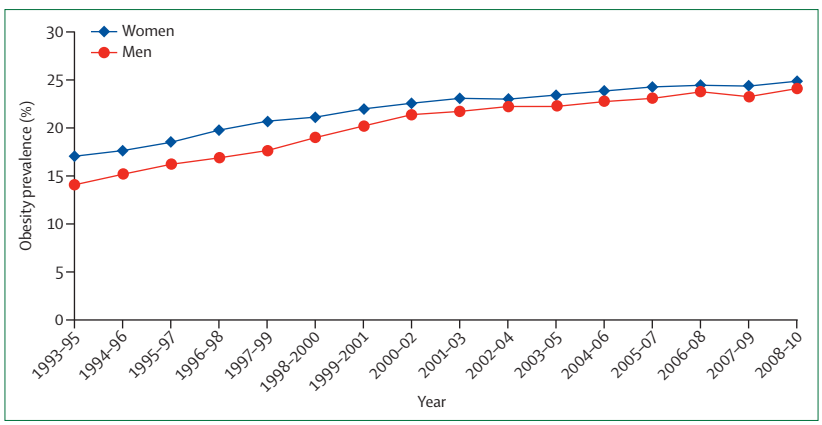

Figure 7: **Prevalence of obesity in men and women aged 16 years or older, 1993–2010**
Data are from Health Survey for England by permission of the Controller of HMSO and the Queen's Printer for Scotland.[60]

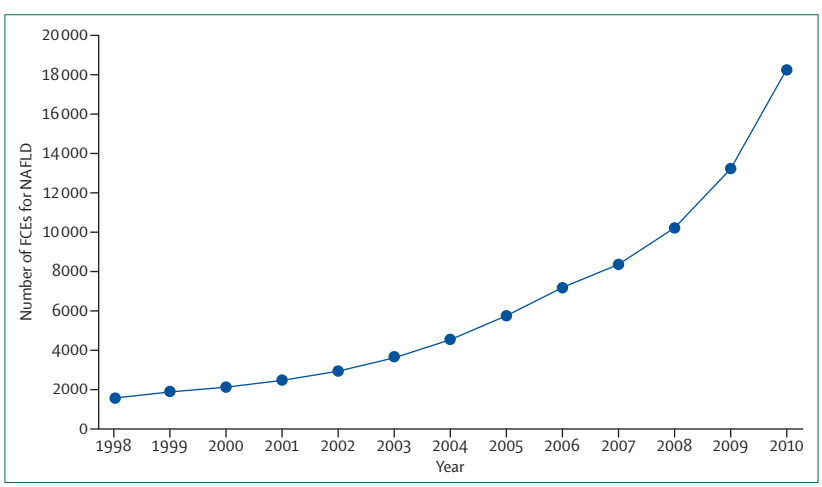

Figure 8: **Number of hospital admissions for non-alcoholic fatty liver disease, 1998–2010**
Admissions to hospital defined as first finished consultant episodes. Data are from Hospital Episode Statistics.[64] FCE=finished consultant episodes. NAFLD=non-alcoholic fatty liver disease.

the two age groups.[58] For children, overweight is classed as the 85th or higher BMI percentile and obesity as 95th or higher BMI percentile for age and sex relative to the British 1990 growth reference. By these criteria, about 22·2% of reception class children and 33·3% of year 6 children are overweight or obese.[59]

In considering the effect on health services of these large numbers of obese adults and children, non-alcoholic fatty liver disease encompasses a range of clinical disorders, from a benign fatty liver (steatosis) to the more serious non-alcoholic steatohepatitis. In NASH, the accumulation of fat in the liver cells is accompanied by inflammation and fibrosis that might eventually progress to decompensated liver disease and hepatocellular cancer. Patients with NASH or advanced fibrosis have an increased risk of liver morbidity or mortality, whereas those with simple steatosis do not. In the context of cardiovascular disease, hepatic steatosis has been identified as an independent risk factor, suggesting the interrelationship between liver fat and wider metabolic effects in the body. Autopsy data suggests 4–9% of people with a BMI of 27·5–35 kg/m² will have NASH, rising to 19% of those with a BMI of more than 35 kg/m²,[53] with the figure of 25% for the present prevalence of obesity (figure 7), this equates to about one in 20 of the UK population having NASH. The Foresight Report[61] predicts a continued rise in rates of obesity so that by 2050, 50–60% of the population will have a BMI of more than 30 kg/m² and hence one in ten of the UK population would have NASH.

Factors affecting development and progression of non-alcoholic fatty liver disease to NASH

Although most factors affecting the risk of development of non-alcoholic fatty liver disease in an individual are environmental, including the level of obesity, presence of diabetes, and extent of physical activity, genetic factors might also have a role in establishing why some individuals are predisposed to depositing fat in the liver and why hepatic steatosis progresses to the more serious condition of NASH in only some patients. Continuing studies of genetic factors have identified specific genes, namely variants of PNPLA3 and TM6SF2,[62,63] which are associated with the progression and development of severe disease including cirrhosis and HCC. Genetic contributions to non-alcoholic fatty liver disease are estimated to be 27–39%.

The absence of any robust survey or screening systems to report the clinical burden of non-alcoholic fatty liver disease or NASH in either primary or secondary care is a major limitation in assessing the effect of these diseases on workload and costs in the NHS. This survey or screening is especially relevant in primary care in which most results from abnormal liver function tests arise from patients with non-alcoholic fatty liver disease.[23] Other consequences of metabolic syndrome, of which non-alcoholic fatty liver disease is the liver component (namely type 2 diabetes, hypertension, and cardiovascular events) represent a substantial burden on the NHS. The limited data available on the natural history of liver disease in individuals with non-alcoholic fatty liver disease or NASH is largely based on findings in secondary care. To define the overall size of the health-care burden of liver disease from non-alcoholic fatty liver disease or NASH in the UK, prospective primary care-based natural history cohort studies need to be established.

Results from the obesity knowledge and intelligence team within Public Health England (formerly the National Obesity Observatory) showed a 12-times increase in the number of hospital admissions in England for obesity-related difficulties and non-alcoholic fatty liver disease between 1998 and 2010 (figure 8). Findings of an analysis by the NHS Blood and Transplant Agency showed that inpatients undergoing liver transplantation, decompensated NASH cirrhosis accounted for a growing proportion of the cases (figure 9; 12% in 2013 compared

with 4% in 1995). According to data from a large UK series,[65] cases of NASH-related hepatocellular carcinoma increased by more than ten times and accounted for 34·8% of all cases of HCC. Moreover, obesity is a well recognised independent risk factor for primary liver cancer and a wide range of non-liver cancers (including breast and colon), showing the substantial burden obesity places on the UK populace.

Case-finding and stratification

At present most patients with non-alcoholic fatty liver disease are identified from blood tests done for other indications in primary care, as suggested in an analysis of a large cohort, funded by the Human Tissue Authority, exploring why GPs checked tests for liver function.[23] After a patient with abnormal liver function tests is identified in primary care as possibly having non-alcoholic fatty liver disease, much uncertainty exists as to which patients should be further investigated. Although in many cases the decision is based on the level of increase of the serum alanine aminotransferase (ALT), this measure has not been shown to relate to the extent of liver fibrosis in most patients who are unlikely to develop substantial liver disease.[66] The BALLETS study[67] showed that non-alcoholic fatty liver disease was the commonest cause of abnormal liver function tests in general practice and identified that a significant proportion of patients (8%) were at risk of having substantial liver fibrosis.[23] Previously, this distinction has been made by use of liver biopsy, although the use of simple algorithms (eg, the aspartate aminotransferase [AST] to ALT ratio[68] in liver function tests and ultrasound modalities such as transient liver elastography[69] in stratifying disease severity) has reduced the reliance on biopsy (table 2). Patients who are obese with slight-fatty liver disease as assessed by normal blood test and liver elastography can be reassured as to their condition without the need for further investigation or hospital referral with respect to liver disease. The need for and timing of additional liver investigations in this low-risk group is unclear, but in view of available natural history data, patients are highly unlikely to develop substantial liver disease in 5–10 years.[71] However, these patients are at risk for other consequences of obesity, especially diabetes and vascular disease. As we recommend in this Commission, all requests for liver function tests from primary care should be returned with an AST/ALT ratio as standard, with an accompanying text for its interpretation. Use of an AST/ALT ratio to identify patients with substantial liver fibrosis, with a cutoff of 0·8, has a sensitivity of 74%, specificity of 78%, positive predictive value of 44%, and a negative predictive value of 93%. The test's greatest value is its high negative predictive value.[68] Many of the non-invasive algorithms used by health-care professionals in the triaging of patients with non-alcoholic fatty liver disease, such as Fibrosis 4 (Fib4), aspartate aminotransferase-to-platelet ratio index (APRI), Enhanced Liver Fibrosis (ELF), and the non-alcoholic fatty liver disease fibrosis score include the AST and ALT values, but are complex, albeit with better test characteristics. National guidelines are needed for the efficient triage of patients to reduce inappropriate referrals to hospital and identify those patients with substantial hepatic fibrosis that do need referral for further investigation.

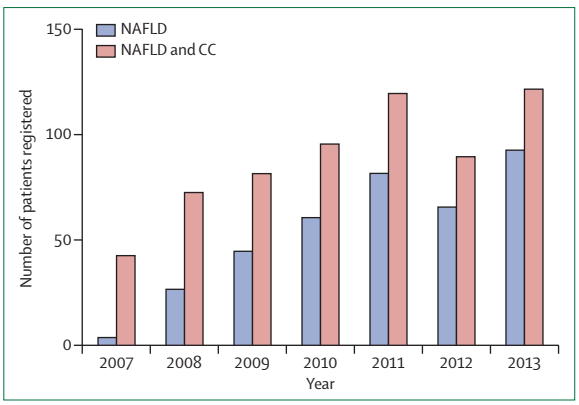

Figure 9: **Number of registrations for liver transplantation in the UK in which primary or secondary diagnosis was non-alcoholic fatty liver disease or cryptogenic cirrhosis**
Data were provided by the UK National Health Service Blood and Transplant (personal communication). NAFLD=non-alcoholic fatty liver disease. CC=cryptogenic cirrhosis.

	Simple algorithms of routine tests		Transient elastography (≥8·7 kPa)		
	Components	Cutoff	PPV	NPV	Prevalence
APRI	AST, platelets	≥1·0	0·13	0·96	0·05
Fib4	Age, AST, platelets	≥1·3	0·13	0·96	0·05
AST/ALT	AST, ALT	≥1·0	0·09	0·95	0·05

A community study of 831 patients with type 2 diabetes in Edinburgh compared with the various algorithms of routine tests as surrogate markers of liver fibrosis, including transient elastography as the gold standard.[70] Raw data were provided by Jo Morling (University of Edinburgh, personal communication) enabling comparative PPVs and NPVs to be calculated in comparison with transient elastography as the gold standard. PPV=positive predictive value. NPV=negative predictive value. APRI=aspartate aminotransferase-to-platelet ratio index. AST=aspartate aminotransferase. Fib4=fibrosis-4. ALT=alanine aminotransferase.

Table 2: **Routine tests and algorithms compared with transient elastography as surrogate markers of liver fibrosis**

Treatment strategy for non-alcoholic fatty liver disease and specific medical measures

Patients with NASH are recommended to be referred to a metabolic liver clinic with a focus on this disease. Such metabolic liver clinics are multidisciplinary in their constitution and contain dietetic, diabetic, and hepatological input, which can provide a standardised approach to the further investigation and management of such patients. Additionally, they will often have established links with weight-loss services both in the community and hospital and will be able to consider patients for continuing clinical trials.

***Panel 5:* Commissioning model for obesity services in England**

- Tier 4: specialised complex obesity services (including bariatric surgery)
- Tier 3: a primary or community care based multidisciplinary team to provide an intensive level of treatment input
- Tier 2: primary care with community interventions
- Tier 1: primary care and community advice

The present commissioning model for obesity services in England[72] is for tier one and two services to be commissioned by local authorities, tier three by the clinical commissioning groups, and tier 4 by specialist commissioning (panel 5). This separation of services could generate barriers to continuity of care and strong integration is important to ensure strong integration across the pathway.

The rapid emergence of new classes of therapeutic drugs for non-alcoholic fatty liver disease such as obeticholic acid, apical sodium-dependent bile acid transporter inhibitors (ASBTi), and GLP-1 analogues, is an exciting development for the specialty and will necessitate the recruitment of patients to clinical trials for completion. Carbohydrates induce non-alcoholic fatty liver disease and a reduction in sugar consumption, especially fructose, is important. Metabolic liver clinics will play an important part in the implementation of such treatments and will need to define quality standards for care and outcomes of such patients to ensure a standardised approach.[73] Reports from the Academy of Medical Royal Colleges and the Royal College of Physicians have addressed these issues and added to the actions already outlined in government policies, such as *Healthy Lives, Healthy People* in 2010. Nevertheless, knowledge and understanding by the general public about non-alcoholic fatty liver disease and NASH is poor, emphasising the need for more professional and public awareness that non-alcoholic fatty liver disease or NASH are serious additional disease risks from being overweight or obese. Clinical guidelines that set out standards of care for non-alcoholic fatty liver disease are needed to support commissioning by Health and Wellbeing Boards, Clinical Commissioning Groups, Public Health England, and NHS England. These standards should be developed together with the commitment of local budget allocations and commissioning of weight management services and should include both early intervention programmes and provision for severe and complicated obesity, including bariatric surgery. Cost-effective commercial organisations should have an important role too by running evidence-based weight management programmes for children and adults.

For the ***Healthy Lives, Healthy People* policy** see https://www.gov.uk/government/publications/healthy-lives-healthy-people-our-strategy-for-public-health-in-england

Population level approaches to reduce obesity prevalence

The greatest effect on non-alcoholic fatty liver disease will come from reducing levels of obesity across the population, which in recent years have been driven by changes to the social, cultural, economic, and physical environments. Changing the so-called obesogenic environment to reduce the energy consumed from food and increase opportunities for regular physical activity will need concerted action at all levels from local to national, individual to population, and across all ages. In the Academy of Medical Royal Colleges report,[74] several measures were proposed including a minimum 20% tax on sugary soft drinks, unified food labelling, nutritional standards in all schools, a ban on television advertising of unhealthy foods before 9 pm, and promotion of walking and cycling. Mexico has led the way on this change with introducing legislation in October, 2013, to impose an 8% tax on foods with an energy content of more than 275 kcal per 100 g. A light touch and voluntary approach towards the food industry is unlikely to have a major affect on the epidemic; the UK Government measures need to be strengthened, including the introduction of regulations and fiscal measures on the food industry, restrictions on marketing, and engagement of schools and employers. Alignment with other policy drivers, such as the need to reduce carbon emissions, provides other important opportunities with effects on both the food supply and physical activity.

How to tackle obesity and all its effects on health, including liver disease, presents an enormous set of challenges, but there seems to be an increasing public and political will to do so. A sufficiently powerful response, with determined action from individual level treatment to upstream population level determinants, should prevent what could be an otherwise inexorable rise in the health burden and would produce major health benefits. Although much remains to be learnt about non-alcoholic fatty liver disease in terms of liver disease, its association with the severe results of metabolic syndrome is well established and the cost burden is well known. In our view, reducing the prevalence of obesity in the population has to be a high priority on the government's agenda for the nation's health (panel 6).

Excess alcohol consumption

Although alcohol is the main risk factor in only a few patients seen with disordered liver function in the community or outpatient clinics, it nonetheless dominates the other risk factors and causes in those who present with serious liver disease and die in hospital. This anomaly is partly indicative of the fact that liver disease from alcohol, particularly of the causes of cirrhosis, often causes symptoms only very late, when decompensated liver disease is already established, and partly because this group of patients, once identified, might not attend regularly for surveillance.

The importance of the effects of harm from alcohol to the liver and to wider aspects of health in the UK is emphasised by two crucial factors that are both of importance to present governmental policies. First, alcohol causes premature avoidable death and is the biggest risk factor for death in men younger than 60 years. Second, a steep social gradient exists for alcohol-related death, with the poorest in society bearing the biggest burden, making this a key issue of health inequality.[75]

Primary prevention strategies

Strategies to address the huge burden of liver disease in the UK can be considered under primary prevention (reducing the per person consumption of alcohol in the population), early identification of those with asymptomatic and reversible liver disease, and finally, improved care for those with established, symptomatic and advanced alcoholic cirrhosis.

Although drinking patterns and alcohol consumption in a community are not normally distributed and 20–30% of the population accounts for 70–80% of the alcohol consumption, there is strong evidence that the burden of harm in a community is linked to the average per person consumption.[13] Hence, the stark rise of consumption in the past half-century in the UK has been followed by a rise in deaths from cirrhosis, and the changing age and sex patterns of consumption has been reflected in the pattern of deaths. Countries, such as France and Italy, that have achieved a sustained decrease in per person consumption during the same period, have reported a proportionate decrease in deaths from cirrhosis.[11]

Increases in alcohol duty since 2008 have resulted in a slight fall in per person consumption in the UK in the past few years, which has given the alcohol industry a platform to say additional tougher regulations are not needed. This reduction has been small in comparison with the preceding increase and partly shows the increasing ethnic diversity and attitudes to alcohol in the UK. The use of HM Customs and Excise data for consumption show the average weekly consumption for adults who drink in the UK exceeds the upper recommended limit of 21 units[75] for men; there is no space for complacency in the present situation.

Individuals can be susceptible or resilient to reaching damaging quantities of alcohol consumption as a result of both their present and previous circumstances. Poor quality early childhoods featuring abuse, neglect, or exposure to a household member who themselves developed problematic drinking behaviours, can leave individuals at risk of drinking heavily during adolescence and adulthood (figure 10). Consumption of excess alcohol in adolescents is routinely recorded by national and international surveys—eg, the European School Survey Project on Alcohol and Drugs.[29] This survey[29] reported that 65% of UK teenagers aged 15–16 years had drunk alcohol and 52% stated having had a heavy drinking episode (≥five drinks on one occasion) in the 30 days before the study. People who develop heavy drinking patterns in early life are more likely to develop harmful drinking patterns as adolescents and adults than those who do not drink heavily in childhood.[77] Of individuals aged 16–24 years in the UK, 27% of men and 19% of women had binged (>8 units in men and >6 units in women in 1 day) on at least one occasion in the previous week before being surveyed.[78] Furthermore, between 2000 and 2013 in England, 15 278 people younger than 18 years were admitted to hospital with alcohol-specific disorders.[78]

Interventions to reduce childhood stressors and increase the quality of parenting and early life support have reduced alcohol consumption in adolescents.[76] However, although experiences in early life might change an individual's susceptibility to harmful levels of alcohol consumption, the pressures to consume large quantities of alcohol and the resultant number of individuals adversely affected are mainly driven by the price, availability, and marketing of alcohol. Although some might assert that such a view ignores the cultural affects within the country, these same three factors do drive cultural change. Increased differences between the price of alcohol in bars (on-trade) and supermarkets (off-trade) have led to more people in the UK drinking at home even if they will be going out later to socialise. The effect of the relaxation of closing times of pubs and bars and of subtle youth-orientated marketing on our culture, is clear. An abundance of evidence shows that health-benefiting changes in alcohol consumption cannot be achieved through information and education alone[79] and there is a duty on governments to inform the public about the risks. Although large scale

***Panel 6:* Key recommendations to address lifestyle factors**

1. Establishment of large, prospective, primary-care-based cohorts to establish population-level data for the prevalence and natural history of non-alcoholic fatty liver disease in the UK
2. Triage of patients in primary care for the likelihood of significant liver fibrosis, by inclusion of an aspartate aminotransferase to alanine aminotransferase ratio followed, when indicated, by a more accurate staging of liver fibrosis by use of transient liver elastography and the diagnostic pathway
3. Referral of patients identified with non-alcoholic steatohepatitis and mild or moderate liver fibrosis to designated multidisciplinary metabolic liver clinics, with possible clinical inclusion trials
4. Increase efforts to reduce the prevalence of obesity in the population through measures to promote healthier lifestyles, including taxation of sugar-sweetened drinks and increased regulation of the food and retail industries

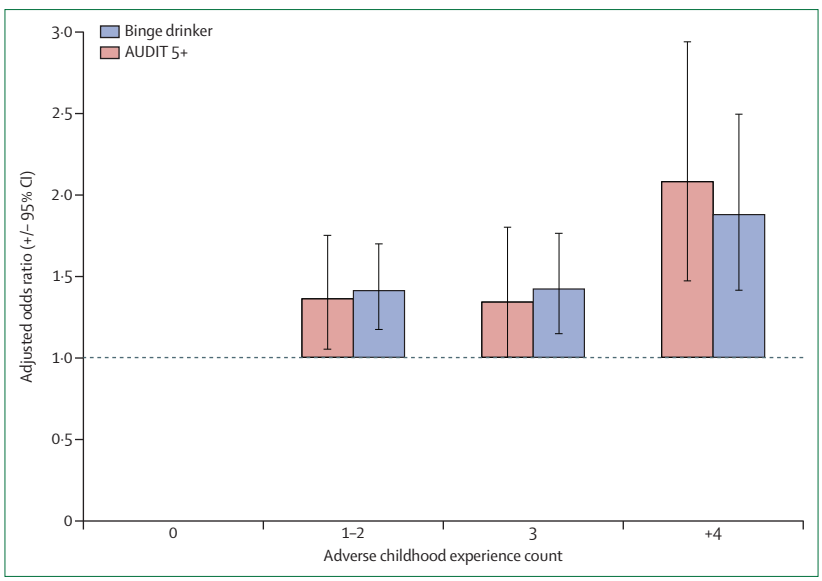

Figure 10: **Relation between adult childhood experience count and regular binge drinking in adults in England**
Odds of the present 5+ AUDIT score. 0 is the reference category. Binge drinking is classified as more than 8 units of alcohol in men and more than 6 units in women in 1 day. Data are from Bellis and colleagues,[76] by permission of *BioMed Central Medicine.*

information initiatives, such as labels of health warnings on products, have been successfully used for tobacco, few countries have mandated for similar strong warnings on alcohol products, so their effectiveness is largely untested.

The most effective method for changing behaviour, whether it be for tobacco, alcohol, or food, is price, and successive governments have used this through direct taxation of alcohol by duty and value added tax (VAT). A duty escalator to increase the price of alcoholic beverages above inflation was put in place in 2008, after which the inexorable annual rise in liver mortality rates in the UK started to plateau. However, as the duty escalator was withdrawn at the 2014 budget[80] in response to industry pressure, death rates from liver disease are expected to rise again (figure 1). Additionally, increasing duty tax does not address the widening gap between on-trade and off-trade prices. A different VAT for on-trade and off-trade would be a possible solution to this problem, but is resisted by the UK Treasury.[81] Another innovative approach, already implemented in Scotland, is a ban on promotions that encourage bulk-purchase (eg, two bottles for £10). A preliminary assessment of this policy after 12 months by the Scottish Government[82] showed a substantial reduction in wine purchases from supermarkets, despite heavy discounting of individual bottles; although an independent review of the policy did not confirm this finding.

Of the actions to directly reduce excessive consumption of alcohol (panel 7), the largest effect will be from tackling the consumption of cheap alcohol by setting a minimum price per unit (10 mL or 8 g of alcohol). This minimum price per unit is in effect setting a floor-price below which it would be illegal to sell alcoholic products, and has the great attraction of potentially targeting the cheapest supermarkets and off-licence alcohol without affecting more reputable brands or the on-trade. The chief medical officer for England supported this suggestion in 2008 in his annual report, at which time modelling by the University of Sheffield predicted a minimum price per unit of 50 pence would save about 3400 lives per year and reduce hospital admissions by 100 000 in England.[83] The Scottish Government has already passed legislation to impose a 50 pence minimum price per unit in Scotland (although this is equivalent to less than 40 pence at 2008 prices), but implementation has been obstructed by a legal challenge from the Scotch Whisky Association. Those who have opposed a minimum price per unit often cite concerns that the policy would penalise people with low-incomes

Panel 7: **Health First's ten recommendations to tackle excess consumption of alcohol in the UK[62]**

- A minimum price of at least 50 pence per unit of alcohol should be introduced for all alcohol sales, together with a mechanism to regularly review and revise this price
- At least a third of every alcohol product label should be given over to an evidence-based health warning as specified by an independent regulatory body
- The tax on every alcohol product should be proportionate to the volume of alcohol it contains. To incentivise the sale of lower strength products, the rate of taxation should increase with product strength
- Licensing legislation should be comprehensively reviewed. Licensing authorities must be empowered to tackle alcohol-related harm by controlling the total availability of alcohol in their jurisdiction
- The sale of alcohol in shops should be restricted to specific times of the day and designated areas; no alcohol promotion should occur outside these areas
- All alcohol advertising and sponsorship should be prohibited. In the short term, alcohol advertising should only be permitted in newspapers and other adult press and the content should be limited to factual information about brand, provenance, and product strength
- An independent body should be established to regulate alcohol promotion, including product and packaging design, in the interests of public health and community safety
- The legal limit for blood alcohol concentration for drivers should be reduced to 50 mg per 100 mL
- All health and social care professionals should be trained in routinely providing early identification and brief alcohol advice to their patients
- People who need support for alcohol problems should be routinely referred to specialist alcohol services for comprehensive assessment and appropriate treatment

and middle-incomes who are so-called responsible drinkers, but these arguments did not stand up against an assessment[84] commissioned by the government (figure 11, table 3). Minimum price is effective because very heavy drinkers tend to graduate towards purchasing the cheapest alcohol available. In a 2014 Government study, patients with alcohol-related cirrhosis drank an average 150 units (five bottles of vodka) a week but only paid 33 pence per unit compared with £1·10 for low-risk drinkers.[14] As a result, the financial effect of a minimum price per unit on these patients would be 200 times greater than for low-risk drinkers (figure 11), supporting findings from the modelling that shows that minimum price per unit targets the heaviest drinkers from all income brackets and mostly under-age (younger than 18 years) drinkers.[85] The benefits of having such a floor-price have been shown in Canada, where an increase of 10% in price was associated with a 30% reduction in deaths wholly attributable to alcohol within 12–24 months.[84,86]

Just as alcohol has become cheaper, availability has increased to 24 h a day 7 days a week both for off-trade and on-trade. Licensing laws were revised in 2004 with the aim of moving the UK to a continental style of culture by relaxing closing times and, importantly, removing the requirement to take into account public health when granting licences to sell alcohol. Although evidence links availability and harm, such as in violence around retail outlets,[87] this trend to deregulation has continued. Even florists and hairdressers are able to serve alcohol to customers, and pubs are allowed at motorway service stations. Some additional powers have been granted to local authorities, such as late night levies, but pressure from the alcohol industry has made implementation difficult. Moreover, in Scotland (but not England), licensing legislation has public health as one of its objectives. Introduction of this objective into the English licensing system would enable licensing panels to refuse applications or attach conditions to them on the basis of the possible effects on the health of the local community. However, effective legislative change also needs political and financial investment in its implementation and enforcement; existing legislation to prohibit the sale of alcohol to people who are already drunk, and who as a result could harm themselves or others, is rarely enforced with typically less than 12 prosecutions nationally in any year.

Finally, marketing, which is subtle, pervasive, and often directed at young people, has changed the patterns of UK drinking and has driven the rise in cirrhosis.[88,89] Several evidence-based reviews[90] reported that children exposed to alcohol marketing started drinking at a younger age and drank more than those who are not exposed to alcohol marketing. Despite existing regulations, 10–15 year-olds in the UK watch substantially more television advertising for alcohol than their parents did when they were children, and children are also heavily exposed to sponsored sport and music events.[91]

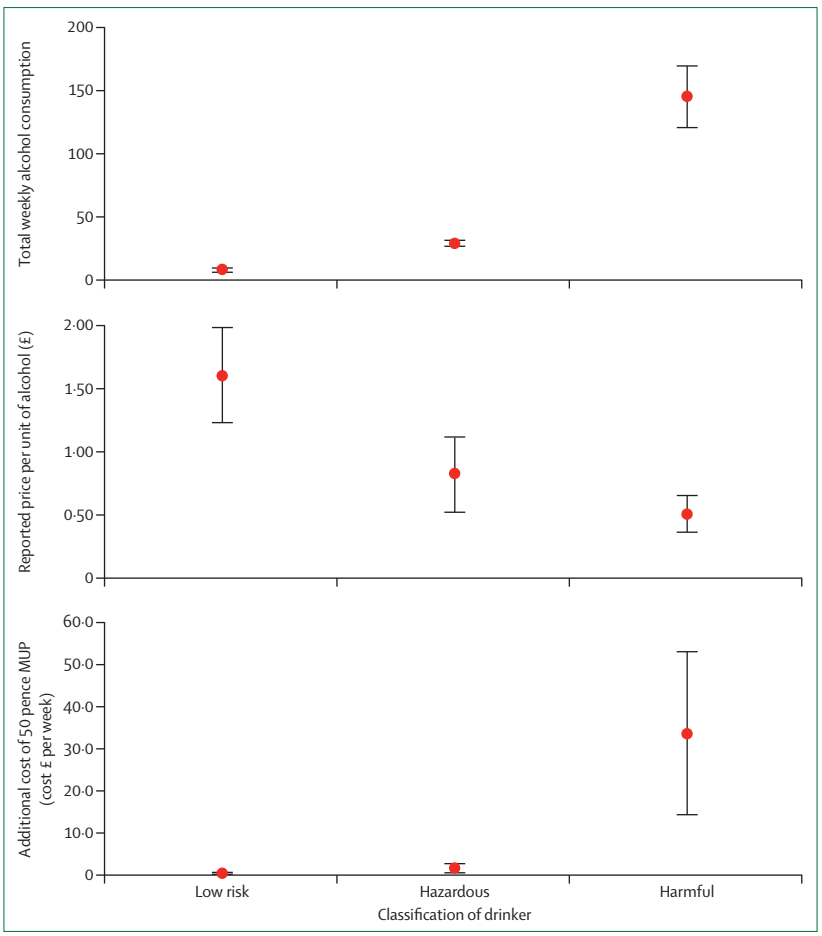

Figure 11: **Mean weekly alcohol consumption, price paid per unit of alcohol, and effect of a 50 pence minimum unit price per unit on categories of drinkers**
404 patients with liver disease categorised according to their level of alcohol drinking as either low risk, harmful, or hazardous. Figures in 95% CI. MUP=minimum unit pricing.

	Moderate		Hazardous		Harmful	
	Low-income	High-income	Low-income	High-income	Low-income	High-income
Reduction in alcohol consumption (%)	−2·3%	−0·6%	−4·4%	−0·5%	−10·6%	−3·6%
Annual reduction in units drunk	−6	−2	−62	−8	−420	−130
Change in spending on alcohol (%)	+2·7%	+0·9%	+1·1%	+2·0%	−1·5%	+1·2%
Annual change in expenditure on alcohol	+£1·70	+£2·80	+£11·50	+£23·20	+£39·90	+£33·50
Reduction in alcohol-related deaths	−7	−12	−108	−21	−442	−370
Reduction in alcohol-related admissions to hospital	−1400	−900	−2900	−800	−17 400	−11 500

Table 3: **Predicted effects of a minimum unit price on different categories of drinkers in the UK[84]**

Worldwide, evidence-based policies have been used to a varying extent, whereas the UK Government has relied on voluntary partnerships with the drinks industry, such

as in the Responsibility Deal.[92] The weaknesses of the flagship deal to reduce consumption by a billion units have been exposed,[93] as has the effect and access of these producers and retailers to politicians.[94]

Secondary prevention strategies

From the perspective of liver disease induced by alcohol, prevention of irreversible histological damage to the liver is the goal. Strong evidence shows that early identification and intervention by a structured interview (identification and brief advice) at a stage when individuals are drinking a hazardous amount, is both successful and cost effective in reducing consumption in the context of many settings, such as primary care and emergency departments.[95] The brief intervention idea comprises of offering feedback about alcohol use and harms, identification of high risk situations for drinking and coping strategies, increased motivation, and the development of a personal plan to reduce alcohol consumption. Evidence shows that most patients with liver disease are able to stop drinking when advised appropriately by a liver specialist;[29] therefore, the aim should be to identify patients at risk early by them recording their drinking habits, and where appropriate, by assessment and staging of liver disease. Technological advances in the non-invasive assessment of liver fibrosis mean that GPs could now diagnose the disease in its early stage. Findings of a study[96] showed that up to 65% of patients with early liver disease stopped drinking at harmful or dependent levels simply as a result of being informed of the diagnosis. Interventions through specialist alcohol treatment services are evidence-based and cost effective, but are restricted in their locational availability.[78] A recommendation was made by NICE[97] about the use of oral nalmefene to reduce cravings for alcohol and the quantities of alcohol consumed by moderate drinkers. However, such a drug or others, including acamprosate, should only be used after the institution of appropriate counselling or brief intervention. Although such secondary prevention might be associated with remission from health-harming quantities of alcohol consumption, individuals who have had treatment will continue to be exposed to cheap alcohol and unprecedented amounts of advertising, which decrease any resolution to drink less.

Another area of innovative success in secondary prevention that needs to be widely implemented is intervention when the patients are at their most susceptible to health messages, namely when admitted to hospital, through multidisciplinary alcohol care teams. The 2001 report[47] by the Royal College of Physicians recommended these teams and have been assessed for their effectiveness. The NHS Quality Innovation Prevention and Productivity programme[45] emphasised how this intervention could save health-care resources.

Reduction of hospital mortality from alcoholic liver disease

Our proposed blueprint for hospital services for liver disease is based on enhanced expertise and facilities for acute care in liver units in district general hospitals. Additionally, more specialist centres to which patients with difficult liver issues can be referred should be fairly placed around the country, which should reduce the high mortality associated with cases of alcoholic liver disease. All the issues raised in the NCEPOD report[2] are specifically addressed in the proposed blueprint through improvements in staffing, availability of ITU, endoscopic care, and alcohol care teams in hospitals which would act as a bridge between hospitals and GPs and community services.

Summary of strategies

The evidence base for reducing physical harm from alcohol, particularly liver disease, is overwhelming and the pervading effects of the alcohol industry[95] need to be matched by stronger government guidance and action. The evidence[46] has been comprehensively reviewed by the UK Alcohol Health Alliance and the University of Stirling and we strongly endorse their recommendations (panel 7).

Viral hepatitis (hepatitis B and C): new opportunities for eradication of infection

Emerging treatments (well tolerated, all oral treatments) for chronic infection of hepatitis C virus will achieve cure rates of about 90%. Present treatments for chronic infection with hepatitis B virus control viraemia and can lead to a reversal of liver damage including cirrhosis. In view of these treatments, the UK now has the ability to eliminate morbidity and mortality from these infections. Appropriate services will need to be developed to deliver this unique opportunity that in the long term will lend to major health-care savings. With the high costs of the new drugs, even if renegotiated, that treatment is unlikely to be completely handed over to the GPs, especially with the continued need for specialist hepatology input in the assessment and management of chronic hepatitis. Furthermore, if because of cost constraints for new drugs, NICE recommends continuation of interferon-based regimens for specific genotype or clinical situations, compliance and adherence by patients could become a major problem.

Intervention effectiveness of antiviral treatment for hepatitis C virus

In the UK, the key groups at risk of hepatitis C virus are people who inject drugs, migrants, and men who have sex with men.[98] 160 000 people are estimated to have chronic hepatitis C virus in England[99,100] (about 0·6% of adults aged 15–64 years). Most infections are reported in people who inject drugs or who have injected drugs in the past, often many years before.

Clearance of the virus from the blood and achievement of a sustained viral response (hepatitis C virus RNA negativity at 3 months after completion of treatment) equates, with few exceptions, to a long-term cure.

Established treatments for hepatitis C virus are based on a combination of peg-interferon (IFN) ribavirin, and the first generation protease inhibitors teleprevir and boceprevir. These protease inhibitors give a sustained virological response in up to 70% of patients, but are often poorly tolerated and are less effective in patients with advanced liver disease. Treatment will be transformed by the licensing of a range of highly effective oral antiviral treatments that can be used without interferon. The combination of sofosbuvir plus an NS5A inhibitor (either daclatasvir or ledipasvir) leads to viral clearance in more than 90% of patients.[101] Sofosbuvir and ledipasvir are available as a combination tablet and in a phase 3 clinical trial[102] of patients with genotype 1 infection, after only 8 weeks of well tolerated treatment, led to 95% of patients achieving a sustained virological response. Alternative regimes (including the AbbVie 3-dimensional combination[103]) have achieved similar response rates with short duration, well tolerated, oral treatment and several other options are progressing through clinical trials. For genotype 2 infections, sofosbuvir plus ribavirin for 12 weeks is highly effective,[104] and similar effective regimes for the other genotypes are likely to be available soon, although genotype 3 infection is less responsive than the other genotypes and might need novel NS5A inhibitors in combination with sofosbuvir. Trials of such genotype 3 specific regimes are expected to start soon, suggesting that a cure for all hepatitis C virus genotypes will be available in the very near future.

The ability to cure hepatitis C with patient-friendly regimes allows consideration of a programme to eliminate hepatitis C virus from the UK. With around 200 000 people infected with hepatitis C, a sustained increase in treatment rates of people at risk of transmitting the infection would lead to a massive reduction in prevalence.[99,105] In fact, an opportunity now exists to almost eliminate this infection from the UK leading to long-term health benefits and cost savings. For example, scaling up the treatment rate of hepatitis C virus to 30–40 per 1000 people who inject drugs with 60% coverage of opiate substitution treatment and needle-exchange programmes, would reduce prevalence of hepatitis C virus by 75–90% in 10 years.[26] Audits of the programme suggest that vaccinations might be missed and that follow-up to check infection status continues to be poor.[106–108]

However, the new drugs are very expensive and in view of the sparse resources, patients will need to be prioritised appropriately. Patients with cirrhosis who are at imminent risk of premature death are one such group, and targeting active drug users will be highly cost effective because it will reduce the onward transmission and lessen the future disease burden. To effectively manage expectations and patient throughput a coordinated national effort will be needed. In 2014, NHS England introduced a scheme in which 500 patients with decompensated cirrhosis will receive sofosbuvir plus an NS5A inhibitor (either daclatasvir or ledipasvir provided for free as part of an expanded access programme by the companies BMS and Gilead, respectively). The programme is in progress and is initially being delivered by 16 centres (table 1), and we believe this will need to be rapidly expanded to 30 treating centres throughout England to supervise local treatment in a network pattern of delivery. This model of care, which includes central multidisciplinary meetings whereby the optimum treatment is agreed with local delivery of treatment, has worked well for the management of malignant disease. Success of the early access programme suggests that this model of care has the ability to deliver highly cost-effective care for patients with hepatitis C. At the time of publication in November, three of the new direct acting antivirals (DAA) have been licensed for use in the UK and are being judged for use by NICE. By mid-2015, as many as eight drugs of high effectiveness will probably be available on the market. The key challenges and opportunities are to develop strategies that can deliver treatments for hepatitis C to people not only with manifestations of severe disease, but also to those with early stage disease (in whom complete restoration of liver histology is likely to result from viral clearance) and to people at risk of transmitting infection to others, such as people who inject drugs and men who have sex with men.

Case finding of hepatitis C virus in at risk populations will probably be cost-effective in primary care.[109] People infected with hepatitis C could also be diagnosed in non-traditional settings of primary care, such as community pharmacies, which provide needle exchanges or methadone. Additional robust evidence is needed on what combination of strategies, incentives, and training (such as local service agreements and digital alerts) will be successful in promoting and facilitating hepatitis C case finding in primary care and in high-risk groups, such as intravenous drug misusers and prisoners.

Hepatitis C virus diagnosis and prevention of end-stage liver disease

Most importantly, a national strategy for England should be developed to identify and treat patients with chronic viral hepatitis, along lines of the Scottish HCV Action Plan. Improved data collection on hepatitis C morbidity by the Health Boards has enabled coordinated action to scale-up treatment and prevention initiatives for this infection. In Scotland, about half of the estimated number of people with chronic hepatitis C virus (about 37 600) were diagnosed by 2012, with about a quarter of those attending a liver specialist and 5000 people (13% of total cases and 25% of those diagnosed) being treated. In England the number of people diagnosed is uncertain, but estimates suggest that about 28 000 patients (perhaps 17% of the total) were treated between 2006 and 2011.[110] These low rates of treatment will not slow the rise in end-stage liver disease, which is likely to increase until at least 2030 (figure 12). Furthermore, model projections

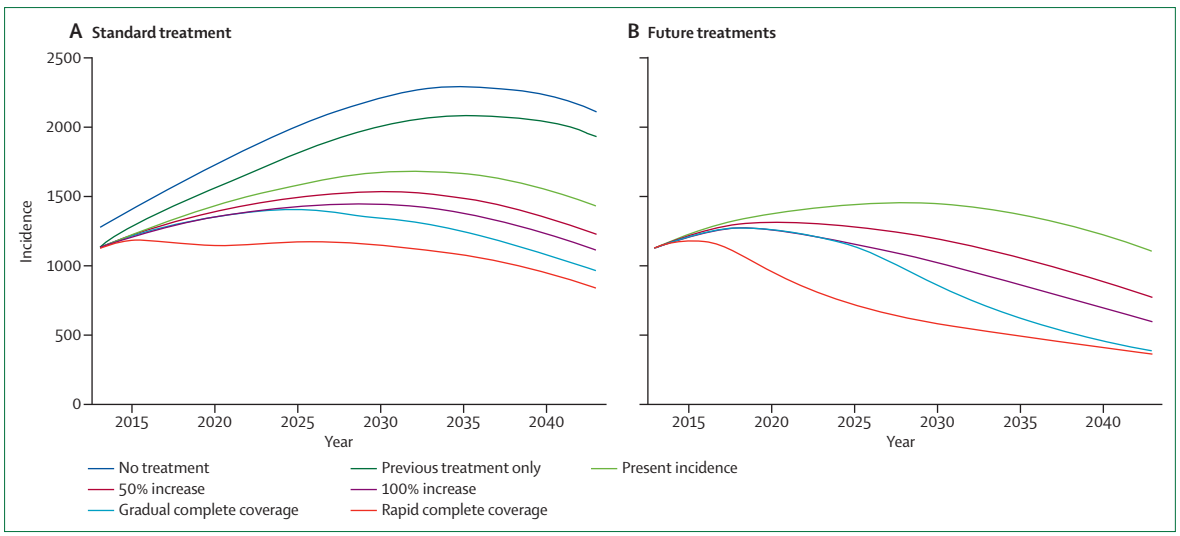

Figure 12: **Predicted annual incidence of end-stage liver disease related to hepatitis C virus and hepatocellular carcinoma**
(A) Different levels of treatment using peg-interferon plus ribavirin. (B) Effects of improved sustained virologic response with interferon free new direct antiviral agent regimes. Figure reproduced from Harris and colleagues,[110] by permission of Elsevier.

suggest that with the continuation of present treatment rates—even with switching to new DAA-based treatment regimens—the number of cases of end-stage liver disease and deaths from liver disease deaths will still increase. Only by scaling-up treatment rates of hepatitis C now (and targeting of people with severe disease) will trends in end-stage liver disease be reversed and the number of deaths be substantially reduced (figure 12).

Prevention of hepatitis C virus in people who inject drugs

Traditional primary prevention methods of opiate substitution treatment and high coverage needle and syringe programmes can reduce transmission and avert infections of hepatitis C.[111–113] However, reduction of hepatitis C virus prevalence through opiate substitution treatment and needle and syringe programmes alone takes a long time and major increases in the number of these programmes are unlikely to be sustainable. Model projections suggest that to reduce prevalence of hepatitis C virus in people who inject drugs by more than 40% in 10 years needs both the introduction and scale-up of hepatitis C virus treatment (figure 13).[26] Furthermore, a positive feedback exists between hepatitis C virus treatment, opiate substitution treatment, and needle and syringe programmes—ie, together they achieve greater reductions in prevalence of hepatitis C virus than they do as separate treatments. Because opiate substitution treatment and needle and syringe programmes are scaled up, fewer treatments for hepatitis C are needed to achieve target reductions in hepatitis C virus prevalence and vice versa.

Present treatment rates of people who inject drugs in England are unknown whereas in Scotland treatment is monitored. An assessment[114] of selected treatment units reported highly heterogeneous rates of treatment with four times the difference in the number of people who inject drugs treated (from <5 to about 25 per 1000 people who inject drugs per year). These rates are insufficient to record a reduction in prevalence and disease burden of hepatitis C. Model projections show that an achievable increase in rates of treatment for hepatitis C virus in people who inject drugs in the UK could lead to substantial reductions in prevalence. For example, in several sites such as Edinburgh, Dundee, Nottingham, and Plymouth, a doubling of treatment for hepatitis C would halve the prevalence and incidence of this virus in 10 years.[26,105] Generally, sites with a high background prevalence of hepatitis C virus need intensive interventions and high treatment rates to generate substantial notable reductions in the prevalence of hepatitis C virus. Nonetheless, in all sites in the UK, an achievable scale-up of hepatitis C virus treatment and other primary interventions could prevent hepatitis C transmission and reduce hepatitis C prevalence and morbidity. Scaling up hepatitis C virus treatment among people who inject drugs is helped by colocating specialist drug treatment and hepatitis C virus treatment services and will be an important consideration for the designated treatment centres.

Observational data and economic models have shown that concerns about re-infection and poor compliance in people who inject drugs are unfounded.[115] Treatment of hepatitis C virus among people who inject drugs is cost effective because of the benefits to the individual and secondary infections are averted. Indeed, in some settings treatment of people who inject drugs is more cost effective than treating people who used to inject drugs or other risk groups.[109] The key question is, in view of scarce resources, which patients should be targeted as treatment is expanded and who can wait? New model

projections of the incremental costs and benefits of treatment prioritisation compared with delayed treatment until the stage of compensated cirrhosis, suggest that only in populations with very high chronic prevalence of hepatitis C (≥60%)—which is no longer the case in the UK—is treatment cost effective for people with moderate disease who do not inject drugs because of high levels of re-infection among populations of people who inject drugs. In populations with 20% and 40% chronic hepatitis C virus in people who inject drugs, the most cost effective approach is to target people with moderate or mild forms of disease who inject drugs before targeting people who do not inject drugs with moderate disease. Therefore, in the UK both disease stage and risk factor should be used to prioritise treatments.

Prison is another important setting for detection of people infected with hepatitis C virus and especially for people who inject drugs. An average sentence served by people who inject drugs in prison is shorter than 6 months and present continuity of care with community and interventions between prison and community is uncertain and underdeveloped. Newer, short duration treatments would allow a larger proportion of people to start and complete treatment within their prison sentence. The tripartite agreement[116] between the National Offender Management Service, Public Health England, and NHS England set a target for the implementation of an opt-out screening for blood-borne virus in 2013. The roll-out for this screening has been delayed because of concerns about the funding of additional tests. 12 so-called pathfinder prisons have been working towards opt-out testing since April, 2014, and an impact assessment is being undertaken later in 2014. Many new diagnoses of hepatitis C are expected to be made as a result of this initiative, leading to an increased number of referrals for treatment.

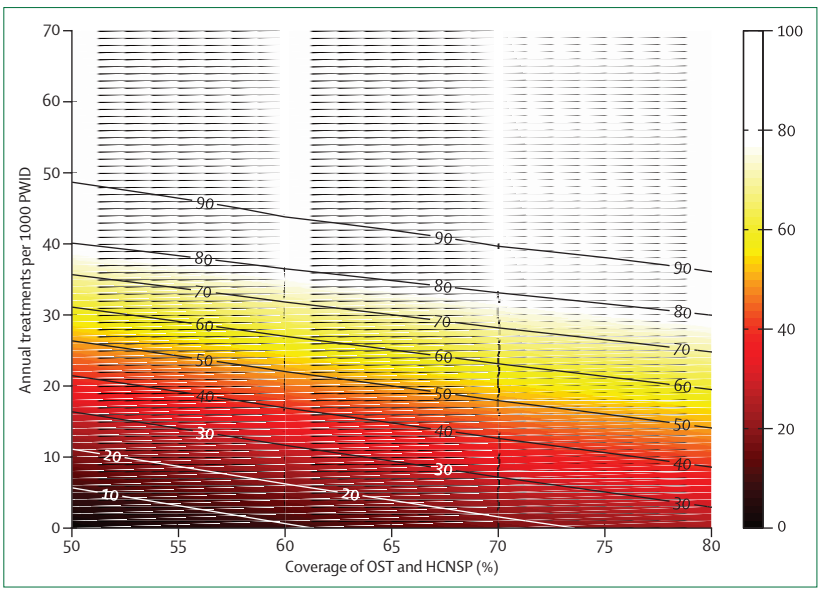

Figure 13: **Modelling projections of the combined effects of antiviral treatment for hepatitis C virus**
Use of direct antiviral agents therapy per 1000 people who inject drugs, OST, and HCNSP programmes on hepatitis C virus prevalence during 10 years in a population of people who inject drugs with 40% chronic hepatitis C virus. Model projections assume a 90% sustained virologic response with future direct antiviral agent therapy. Gradient lines show percentage reduction for specific combination of hepatitis C virus antiviral treatment and OST and HCNSP. Heat colours show levels of hepatitis C virus reduced from 0 (dark) to more than 80% (white). Increases in OST and NSP reduce need for hepatitis C virus treatment to achieve target reductions. PWID=people who inject drugs. OST=opiate substitution treatment. HCNSP=needle and syringe programmes. Adapted from Martin and colleagues,[26] by permission of *Clinical Infectious Diseases*.

Hepatitis B virus

Unlike hepatitis C virus, an effective vaccination exists against hepatitis B virus[117] and vaccination coverage for hepatitis B virus in people who inject drugs has increased as a result of prison programmes. Hepatitis B chronic disease if acquired is manageable, because treatment options can suppress hepatitis B virus replication sufficiently to prevent progression of disease. Such treatments, unlike those for hepatitis C virus, eradicate the virus from the body owing to persistence of viral nuclear material known as covalently closed circular (ccc) DNA in the hepatocyte nucleus. Transmission of hepatitis B perinatally from mother to child usually leads to chronic infection, whereas transmission between adults through sexual and parenteral routes typically causes an acute, self-limiting infection, and clinical illness. Although the number of people with chronic infection of hepatitis B virus is unknown, the figure is probably similar to those with hepatitis C virus. An estimate from 2002 suggested 180 000 people had chronic hepatitis B virus, whereas another gave a figure of more than 320 000 for the same year;[118] neither estimate is strongly evidence based. Most infections with chronic hepatitis B virus are likely to be among migrants coming into the UK who acquired their infection in childhood from their native country. For instance, a study of cases of chronic hepatitis B virus in 1995–2000 estimated that about 95% of infections were in migrants[119] from countries with high prevalence rates of hepatitis B infection (2–8%). Increases in the prevalence of hepatitis Δ infection in parts of the country, such as south London, is related to large numbers of immigrants from Africa where Δ coinfection is common.

Primary prevention

In populations with moderate to high endemic levels of hepatitis B virus,[120] universal infant vaccination substantially reduces the prevalence of chronic hepatitis B virus and complicating liver diseases, including HCC. In the UK, horizontal transmission during childhood, even in high-risk children, is low, and the introduction of universal vaccination has, so far, been resisted because of lack of proven cost effectiveness,[121] although this has been deemed cost effective in other European countries with a similar prevalence of hepatitis B and immigrant population. Additionally, so-called invisible benefits of universal vaccination whereby this vaccination raises awareness in GPs and avoids the societal effect of

Panel 8: **Recommendations for addressing levels of viral hepatitis B and C infection**

1. Highly effective and safe, direct acting antiviral drugs for hepatitis C virus are available and a national strategy to identify more of the presently unidentified patients with chronic hepatitis should be developed, focusing initially on those who are most likely to transmit infection, such as injecting drug misusers and prisoners
2. Ambitious targets should be set locally and nationally to eradicate liver disease caused by hepatitis B and C virus in 20–30 years; to reach this target, improved case finding of asymptomatic individuals and those infected with hepatitis B or C virus, with particular attention to immigrant populations is needed
3. Antenatal screening for hepatitis B virus and immunisation of babies born to mothers infected with the virus is cost-saving, but at present is poorly administered; universal hepatitis B virus vaccination should be introduced once a safe and effective six-in-one infant vaccine schedule becomes available
4. Immigrants from countries with high prevalence of infections of hepatitis B or C virus should be targeted for extensive case-finding both in primary care and at the time of pre-entry visa application

immigrant to native transmission events are impossible to quantify. The low number of cases of chronic disease acquired in the UK also means that a separate schedule for universal vaccination of hepatitis B virus in infants is unlikely to be introduced.[122] However, a low-cost vaccine as a component combined with an existing vaccine (such as the five-in-one given to infants to protect against diphtheria, tetanus, pertussis, polio, and *Haemophilus influenzae* type b) could be cost effective. The issue is to identify a six-in-one combination vaccine that does not inhibit the efficacy of other vaccines, especially *Haemophilus influenzae* type b.[123] It is in the UK's interest also to encourage and support countries with endemically high numbers of hepatitis B virus cases in the provision of universal infant vaccination for hepatitis B virus, especially in countries with high numbers of migrants to the UK.

Antenatal screening, introduced in the UK in 2000 to identify mothers infected with hepatitis B virus (about 0·5%) and then initiating hepatitis B virus vaccination at birth, is highly successful and cost effective.[124,125] Audits of the programme suggest that vaccinations are missed and that follow-up is poor. In view of the high risk of transmission for a cost-saving intervention, failure to vaccinate and follow-up of babies born to mothers infected with hepatitis B should be regarded as a so-called never event in the NHS.

Immigrants to the country represent the largest group of patients in the UK with undiagnosed, chronic hepatitis B virus and should be the target for extensive case finding. Case finding in primary care is probably the best approach although, as with hepatitis C virus, robust evidence on which strategies are best and most effective is scarce.[98] Additional approaches include the screening of immigrants at the time of obtaining a visa for entry to the UK, on the evidence that more than 7000 new people infected with hepatitis B are brought into the country through immigration every year. This approach would be in line with the pre-entry visa screening for tuberculosis introduced by the government in 2012.[126] Although screening immigrants from countries in the European Union (EU) is likely to be regarded as a barrier to the free movement of people and illegal under EU law, most immigrants with unrecognised infection come from non-EU, higher prevalence areas of the world—ie, Asia, Africa, and the Middle East. In addressing the underdiagnosed and undertreated population of people infected with chronic hepatitis B virus who are living in the UK, pilot studies of new strategies offer testing to new registrants of GPs and provide alerts to encourage opportunistic case-finding. Both these strategies need to be extended if the disease burden of hepatitis B virus is to be reduced and, as an added benefit, awareness of the disease increased (panel 8).

Engagement of primary care in detection and management of liver disease

Knowledge and awareness of liver disease in primary care is low with an absence of adequate diagnostic methods and training in the diagnosis and management of the early stages of liver disease. About three-quarters of people with cirrhosis are not detected until they present to hospital with end-stage liver disease, by which time morbidity and mortality is high and the scope for intervention is substantially reduced (figure 14). Despite the long natural history, often decades, of almost all liver diseases with ongoing low grade cellular injury and inflammation results in the gradual development of hepatic fibrosis; if disease is detected there are opportunities to reverse this process. Liver disease arises in highly recognisable groups of patients, but at present no agreed method of screening for liver disease or a standardised bundle of care to manage it, exists. Increased engagement of primary care in the detection and management of the early stages of liver disease is imperative if this disease is to be detected at an early stage and those cases that are at risk of progressive disease are to be identified. The strong associations between risk factors for liver disease and mortality from other major diseases, such as hypertension and diabetes, that share common lifestyle risk factors and in which well developed pathways of care are in place within general practitioner and community services, is not widely appreciated. We strongly recommend the inclusion of liver disease in this group.

Recognition, scope, and nature of liver disorders in primary care

In primary care the three disorders of alcoholic liver disease, non-alcoholic fatty liver disease, and chronic viral hepatitis B and C, account for almost all liver disease. Irrespective of the cause of the liver injury, the conditions are usually asymptomatic and the patient is apparently healthy. However, people who drink to excess are recognised as using primary care more than their peers and are frequently well known to the practice. Most patients with risk factors for non-alcoholic fatty liver disease will already be in screening or secondary prevention programmes for hypertension, diabetes, or cardiovascular risk modification. Addition of a consideration for liver disease to this screening has the potential for major therapeutic gain with only a slight outlay. Chronic viral hepatitis B and C are more likely to be encountered in urban areas, particularly those with many settled immigrants and where intravenous drug misuse is common. Primary care has an important role both in detection and management of these infections which, again, if unrecognised can result in severe liver disease.

Liver function tests and early detection of liver damage

The standard liver function test panel that is provided by laboratories in the UK is of little use in screening for early disease. The panel consists of two true functional markers, namely the serum bilirubin and albumin concentrations, which will not be abnormal until decompensation of liver cirrhosis is either imminent or has already happened. The test also contains the liver enzymes alkaline phosphatase and alanine amino-transferase and when requested, γ-glutamyl trans-peptidase. Although changes in concentrations of serum enzymes are an indication of injury to liver cells, the changes are non-specific for the cause of the liver damage and do not reliably detect developing liver fibrosis or cirrhosis. Notably, up to 90% of people with early alcohol-related fibrosis and 75% of people with severe fibrosis have normal results from liver tests.[127,128] Increases in liver enzymes are too a poor indicator for viral hepatitis infections because at any one time a third of patients with chronic hepatitis C virus, and more for chronic hepatitis B virus, will have a normal concentrations of ALT.[129,130] In a community study[23] targeting patients with risk factors for developing liver disease, advanced fibrosis, and cirrhosis were identified in a substantial number of patients who had normal liver enzyme concentrations.

Thus, existing approaches to abnormal liver function tests do not help GPs to discriminate those patients at risk of progressive fibrosis and in whom a treatment intervention for obesity or excess alcohol consumption would be especially valuable.

Liver disease can be recognised at two key stages. First, identification of probable disease according to risk factor. However, this identification is underused because although common risk factors, particularly metabolic syndrome and obesity, will typically trigger consideration of diabetes and cardiovascular disease, they do not routinely trigger consideration of liver disease. Second, the use of liver blood tests, to establish patients who are developing hepatic fibrosis and are thereby at risk from progression of their disorder, and other diagnostic approaches to identify specific causes including hepatitis B or C and other chronic liver disorders, such as autoimmune hepatitis.

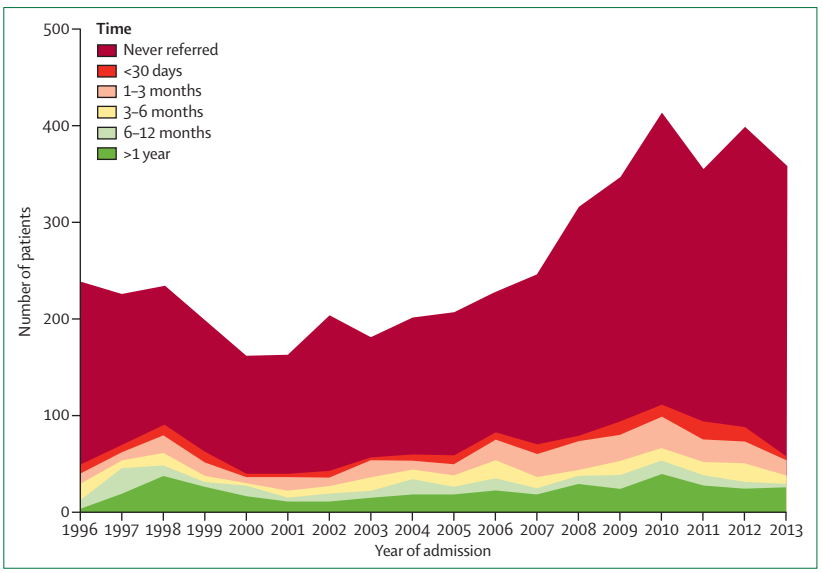

Figure 14: **Time between referral to a liver clinic and the first admission with cirrhosis or liver failure**
73% of patients (red area) had not been referred to a liver clinic before the liver admission, and only 12% of patients (green area) were referred more than a year before their first admission to hospital. Original analysis of 4313 first admissions between 1996 and 2012 with cirrhosis or liver failure by International Classification of diseases-10 code to University Hospitals Southampton, UK. Data are from Emma Greatorex (University Hospital Southampton Trust, Southampton, UK, personal communication). Analysed by Nick Sheron.

Findings of the BALLETS study[67] showed that most reasons for undertaking liver function tests in primary care were in reviewing diabetes and hypertension and non-specific health checks, not because liver disease was suspected. This finding emphasises that the potential for detection of liver disease is already in place. In the BALLETS study,[67] a cause for high liver function test was reported in 55% of participants, of whom 25% had alcohol-related liver disease, 26% had non-alcoholic fatty liver disease, and 3·3% had a specific liver disease such as viral hepatitis, autoimmune liver disease, or rare metabolic liver disorders. In 45% of participants, no specific liver disease could be identified and the tests were normal in 20% of individuals.[67] Other than in people with non-alcoholic fatty liver disease (of whom 7·6% had advanced fibrosis on non-invasive testing), tests for the detection of fibrosis were not routinely done and the overall number of progressive liver fibrosis in the study population was not established.[67]

The rule of screening specific populations who are at high risk of particular liver diseases is endorsed by NICE for hepatitis B and C infections. However, NICE guidance for viral hepatitis B and C testing has not been

For more on **NICE's liver disease guidance** see http://guidance.nice.org.uk/PH43

***Panel 9:* Detection through aspartate aminotransferase to alanine aminotransferase ratio of increasing fibrosis in patients with raised concentrations of liver enzymes**

As cirrhosis develops, the concentration of alanine aminotransferase (ALT) falls in comparison with aspartate aminotransferase (AST), presumably related to a loss of functioning hepatocytes and in patients with non-alcoholic fatty liver disease, the ratio has a reasonable predictive value for the presence of fibrosis.[23] The inclusion of the AST/ALT ratio in liver function tests, and being an opportunity for education on the significance of the results and their use, also narrows the target population of those with abnormal ALT values on which to focus further diagnostic tests for cause and fibrosis stage.

widely applied in primary care nor have the lessons been learned from viral infections that increase concentrations of transaminase is not a reliable marker of liver damage. Such screening uptake would be improved by inclusion of a wider regard of the other lifestyle risk factors. The key is to detect patients at risk of hepatic fibrosis and to minimise the investigation of those at low risk. Common situations in which this question arises are in patients who are incidentally found to have abnormal transaminases, in those who are known to be drinking at hazardous and harmful quantities, and during screening of other populations at risk of liver disease—eg, type 2 diabetes.

In the situation in which abnormal transaminases are found incidentally, the underlying cause is usually obvious; a large consumption of alcohol and metabolic syndrome being the most common. The important issue is whether the patient already has substantial liver fibrosis and is at risk of developing morbidity from liver disease without therapeutic intervention. In a Tayside study[131] in which 95 000 people were followed up for a median of 4 years, findings showed that at least 25% of the general practice population had their liver function tests checked in a decade and about a third had at least one abnormal value. Although minor increases of ALT, alkaline phosphatase (ALP), or γ-glutamyl transpeptidase (GGT) were associated with a 3–5 times increase in liver related mortality and substantial increases with a 7–25 times increase, the actual rate of detection of specific liver diseases was only 1·4%. An issue that continues to cause confusion when detecting liver disease is the widespread use of statins. Although statins can cause concentrations of serum transaminase to increase, their use should almost never be stopped especially because this evidence suggests that statins can prevent the development of hepatic fibrosis.[132]

Screening at risk populations

Early detection of liver disease in general practice by screening programmes can only be justified if it leads to effective treatment or intervention. The value of detecting hepatitis B and C infections cannot be questioned, with the availability of new highly effective treatment regimens that can prevent progression to severe liver disease and in the case of viral hepatitis C, eradicate the infection. Although evidence is scarce for the effectiveness of preventive or treatment options in reducing progression of liver disease from obesity related steatohepatitis through dieting, results of several studies have shown improvement in liver blood tests and in the severity of hepatic steatosis, and with bariatric surgery, a substantial improvement in diabetes control.

The identification of people classed as hazardous or harmful drinkers is worthwhile; results of many studies have shown the efficacy and cost-effectiveness of brief interventions[96] in the reduction of alcohol consumption and in the reversal of early stages of alcohol-related liver disease. With a number needed to be treated of 8–12 people to produce one positive event (stopping harmful drinking),[133] about 10% of people reduce their drinking to safe quantities. Emerging evidence that the effect of a brief intervention is enhanced when coupled with staging of liver disease. One study[127] achieved quantities of safe drinking in 65% of previously harmful drinkers with liver fibrosis after 1 year. Brief interventions can take place within the timeframe of a standard

***Panel 10:* Examples of targeted screening programmes in the UK**

The Southampton Traffic Light procedure

This combines two surrogate markers of fibrosis, hyaluronic acid and collagen P3N peptide, with platelet count. The traffic light grade of red, amber, or green identified liver fibrosis (positive predictive value red light 0·84, negative predictive value green light 0·96) and predicted mortality in 2533 patients who were followed up to 9 years (mean 40 months). In a feasibility study,[134] the simple feedback of a red or amber test result by GPs stopped alcohol misuse in 65% of drinkers classed as harmful or dependent with early liver disease at follow-up after 1 year.[135] Portable fibro-scanning is done by a trained practice nurse and the LOCATE study[135] comparing the Southampton Traffic Light procedure with liver elastography to identify severe fibrosis and cirrhosis in patients at high risk in primary care will be reported in 2015.

The Nottingham study[128]

The concept of targeting risk factors and application of simple blood tests (including the aspartate aminotransferase to alanine aminotransferase ratio) and elastography within the community setting was tested in Nottingham. In a primary care population of 12 368 patients, 920 patients were identified with risk factors, including alcohol and type 2 diabetes. About 400 patients underwent community elastography and 26% of individuals had raised readings; most (70%) had normal liver function tests. The rate of cirrhosis detection was doubled by the use of this approach.[128]

consultation with a GP of 5–15 min or longer for a nurse consultation. Furthermore, the addition of liver elastography to the screening process is very cheap. When a practice nurse uses a portable machine, the cost of elastography is about £20 per scan, less than a tenth of the cost for outpatient referral to a specialist and targeted programmes of screening in the community have been successful (panels 9 and 10).

At present the capacity to substantially expand the engagement of GPs in such programmes is restricted, and funding issues will need to be addressed. The Quality and Outcomes Framework (an annual reward and incentive programmine detailing GP practive achievement introduced in 2004) is being scaled back rather than expanded and the introduction of a new clinical domain is deemed unlikely. Additionally, valuable lifestyle advice indicators were removed in the governments' budget of April, 2014,[80] including the targets of giving people with hypertension advice about smoking cessation, safe quantities of alcohol consumption, and a healthy diet.

Proposed diagnostic pathway in primary care

Key to our proposed diagnostic pathway is the routine inclusion of AST and GGT into the standard panel of tests for liver function when liver disease is clinically suspected. The AST value will enable calculation of the AST/ALT ratio (panel 9), as well as a score in the non-invasive algorithm APRI and other algorithms, in patients with non-alcoholic fatty liver disease. GGT concentration is a marker for alcohol intake and had the highest predictive value in terms of subsequent liver disease and mortality in a large community study.[136] Abnormalities in this enzyme can also

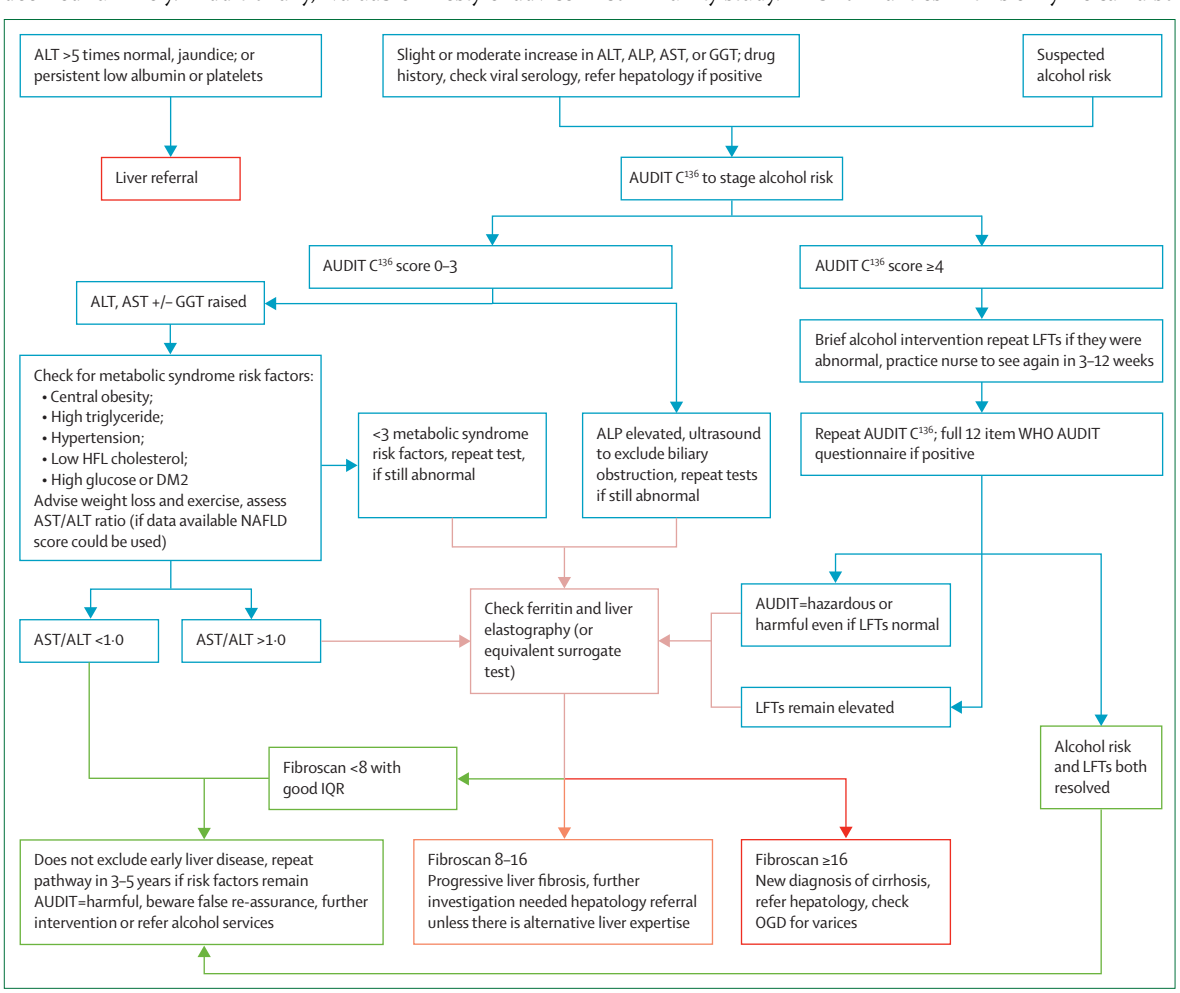

Figure 15: **Diagnostic pathways for liver disease**

ALT=alanine aminotransferase. ALP=alkaline phosphatase. AST=aspartate aminotransferase. GGT=γ-glutamyl transpeptidase. DM2=type 2 diabetes. NAFLD=non-alcoholic fatty liver disease. LFTs=liver function tests. IQR=interquartile range. OGD=oesophogastroduodenoscopy. AUDIT C=Alcohol Use Disorders Identification Test-Consumption; a three question test (taken from the ten question AUDIT) is a screening method to identify hazardous alcohol consumption on a scale of 0–12; a score of 4 or more identifies people who drink hazardously or are at increasing risk, 7 or more identifies people as harmful drinkers or of higher risk, and 9 or more identifies people who are possibly dependent on alcohol. Red represents when secondary care referral is indicated for probable serious liver disease, acute hepatic injury, severe fibrosis, or cirrhosis. Orange represents when secondary care referral is usually indicated for probable progressive liver fibrosis but not cirrhosis. Green represents no evidence of significant liver fibrosis at this stage, risk factors should be addressed and the pathway repeated after an interval if they remain. Blue represents the usual pathway. Pink represents the final decision box. Drafted by Nick Sheron, Philip Newsome, and Steve Ryder.

be used to motivate positive changes in behavioural in people who drink to excess because GGT concentrations rapidly decrease with abstinence from alcohol.[137,138]

Our pathway (figure 15) is based on both results from liver blood tests and an assessment of risk factors for liver disease, such as obesity, excess alcohol, drug misuse, and viral hepatitis. Patients might frequently have several of these risk factors. Both aspects of this assessment need to be considered before substantial liver disease can be ruled out and unnecessary referral of the patient to hospital avoided.

For patients with evidence of metabolic syndrome and increased concentrations of serum transaminases, the value of liver blood tests is enhanced if the commonly used ALT is related to the AST concentration in an AST/ALT ratio. When the ratio is more than 1·0, it is a strong indicator of the presence of fibrotic liver disease. Patients with a high AST/ALT ratio need further investigation by liver elastography and if this fibroscan result is raised to more than 8 kilopascals (kPa), the patient will need to be referred to hospital for consideration of liver biopsy and other investigations. Patients in whom alcohol excess is suspected as the cause should be given a brief intervention by the GP or community nurse as the beginning of attempts to control their alcohol consumption. Similarly, for people who are obese, this step should be the beginning of efforts to improve their lifestyle choices.

If a patient with a raised ALT concentration has a normal AST/ALT ratio, further investigations by liver elastography would be justified only if the patient falls into one of the high-risk categories. The presence of diabetes greatly increases chances of an individual having substantial liver disease and is an important consideration in recommending a patient in this group for further investigation by liver elastography. If the liver elastography result is deemed normal, additional investigation and referral to hospital are unnecessary. However, if the patient is known to have possible causal factors for liver disease—ie, hepatitis C or B virus—a hospital referral for more detailed investigation would be necessary. For this group, patients who are obese with apparently benign non-alcoholic fatty liver disease or who are drinking excessively, but have normal blood tests or liver elastography results, further follow-up can safely be deferred for 3 years for alcohol misuse and 5 years for non-alcoholic fatty liver disease.

Many patients with liver disease do not have abnormal ALT concentrations and screening by liver elastography for the presence of liver fibrosis should be on the basis of the level of risk factor alone—ie, the presence of type 2 diabetes or a long history of drinking excessively. If the liver elastography is normal, then patients should go into the same follow-up path as the previous group. Patients in this group who have a normal ALT concentration and other blood tests and in those who are drinking excessively are likely to have a raised GGT concentration in 30–40% of cases. When an isolated, raised concentration of alkaline phosphatase (ALP) is noted, the concentration of serum GGT helps to distinguish between biliary or liver disease from bone disease and suggests the need for further investigations by ultrasound.

For more on the **Love your Liver campaign** see http://loveyourliver.org.uk/

Use of liver elastography in the diagnostic pathway

Transient liver elastography is the gold standard in the assessment for liver fibrosis. Transient liver elastography directly measures liver stiffness by use of a fibroscan or a modified ultrasound machine and is predictive of liver-related events and death.[140] In a meta-analysis[141] of 7000 patients in more than 50 studies shows the area under the curve analyses (AUROC) for cirrhosis (0·94), severe fibrosis (0·89), or early fibrosis (0·84).

Of algorithms for indirect or surrogate blood tests, the most studied is Fibrotest: 6378 participants in 30 studies Fibrotest assessed in meta-analysis[142] against liver biopsy, AUROC results were 0·69 for cirrhosis, 0·67 for severe fibrosis, and 0·66 for early fibrosis.

A small number of studies have addressed diagnosis of liver fibrosis in community settings.[23,70,127,128,134,143–147] Of these, three[70,128,145] compared community prevalence of liver fibrosis using transient elastography with various alternatives. Surrogate markers consistently detect a high prevalence of liver fibrosis, suggesting higher rates of false positives than with the use of transient elastography; this was shown in a study[70] in which valid comparisons of the positive and negative predictive values could be made (table 2). Compared with transient elastography, the various surrogate markers have low positive predictive values of 9–16% and negative predictive values of 95–96%.

At present, most GPs do not have access to the machines to do liver elastography. However, most new ultrasound machines can be adapted to do liver elastography. This form of assessment should, in our opinion, be included as part of the standard operating procedure for all liver examinations by use of ultrasound requested from primary care. Additional time to include liver elastography per examination is low at possibly 5 min, and extra training needed for the workforce will be small. Furthermore, rapid access assessments by nurses for liver elastography could be organised in the same way that rapid access endoscopy is made available to GPs. Elastography will need to be promoted to the radiological and ultrasound community by the Royal College of Radiologists and British Medical Ultrasound Society. Additionally, portable elastography could be used in the community as reported in the Southampton and Nottingham studies (panel 10). This approach formed part of the very successful Love your Liver workshops organised around the UK by the British Liver Trust successfully raised awareness.

Training and development of expertise in general practices

We recommend focused training in general practices to emphasise the frequency of silent liver disease in patients with obesity, excess alcohol consumption, chronic viral

hepatitis, or rare liver conditions to improve rates of early detection and enable targeted approaches for prevention. Although the Royal College of General Practitioners (RCGP) have online e-learning resources for detection, diagnosis, and management of hepatitis B and C,[148] resources to support the broad rollout of training seem to be inadequate. Nurses based in communities are well placed to incorporate liver health in health assessments and screening by querying patients about risk factors for viral hepatitis and metabolic disorders, eliciting a history of alcohol use, and taking BMI measurements. These nurses can liaise with secondary and tertiary levels of care, identifying liver disease in high-risk patients to promote cohesive pathways of care. The value of this care pathway is shown by established networks of care, such as the Yorkshire and Humber Liver Network, which was created in 2007.

We endorse the introduction of new positions for community hepatologists—ie, who would be GPs with additional training and skills in liver disorders. The knowledge that they would bring to a general practice setting would complement that of other GPs with particular skills in diabetes and cardiovascular disorders.[149] Community hepatologists would enhance effective leadership in driving improved and standardised care through focusing on the need for improvements in training, development of training methods, promoting joined-up care-pathways, and service development. These doctors would also help with issues of clinical commissioning because even if primary care trusts and local authorities draw attention to liver disease through their Joint Strategic Needs Assessment (JSNA), they still need to compete for funding with other priorities in local health. Presentation of a clear case for change that balances cost-effectiveness with improvements in patient care would support commissioners in local decision making. Such appointments of community hepatologists would be consistent with the proposal for liver disease to be made a clinical priority for the RCGP through their clinical priorities programme.[7]

Conclusions

Liver disease has long been viewed as being largely the responsibility of hospital specialists despite the disorder sharing common lifestyle risk factors that relate to many chronic diseases that are managed in primary care. In view of the burden of liver disease, its absence from the list of chronic diseases whose management is led and incentivised by the Quality and Outcomes Framework is incongruous. The shared lifestyle risk factors provide an opportunity to expand the breadth of existing disease monitoring, but without a substantial increase in workload (eg, annual cardiovascular, renal, or diabetic checks that already commonly include liver blood tests) the results are not considered from the perspective of liver disease. Development of clear protocols and schedules for investigation, clarification of referral criteria, and additional training programmes will improve the confidence of primary care workers in the management of liver disease. Identification of liver disease in patients at high risk in communities at an early stage will enable effective behavioural interventions and treatments and will prevent the inexorable progression of liver disease in many cases. Furthermore, by using simple algorithms of existing blood tests to exclude severe liver disease in non-alcoholic fatty liver disease and using portable elastography services led by nurses to identify severe liver disease in primary care, expensive referrals to specialist secondary care clinics can be used more efficiently (panel 11).

***Panel 11:* Recommendations for engagement of primary care**

1. Liver disease should be positioned in primary care within the so-called Big Five chronic, preventable lifestyle-related diseases that share common lifestyle risk factors with cardiovascular disease, diabetes, chronic lung disease, and renal disease to maximise the effects from generic lifestyle interventions and to coordinate chronic disease management with the introduction of an appropriate funding mechanism
2. Liver function tests should include measurement of the aspartate aminotransferase (AST) value to allow the calculation of the AST to alanine aminotransferase (ALT) ratio in all samples with an increased ALT and in the proposed diagnostic pathway, with serum γ-glutamyl transpeptidase concentrations and incorporation of liver elastography as a confirmatory test for hepatic fibrosis would distinguish between patients who are most likely to develop progressive liver disease from those who are not, thereby establishing appropriate referral for secondary care

Paediatric liver services as a model of specialist centre care

Management in paediatric care

Management of paediatric liver disease in the UK, including hepatobiliary surgery and transplantation, is centralised to three national centres, leading to internationally recognised outcomes and high value educational programmes. Children with liver disease are now surviving with a good quality life into adulthood, which will increase the burden for adult providers who will need to become familiar with childhood onset of liver disease.[150] Progress still needs to be made in increasing public and professional awareness of the importance for an early diagnosis of neonatal disease, in improving the interface between primary and secondary care, and in clarifying pathways for transition from paediatric to adult services; our main recommendations for paediatric care. Patterns of excessive drinking in childhood are an increasing issue, which has already

been referred to. In 2010, the mean weekly alcohol consumption of children aged 14 years was more than the safe recommended limit for both boys and girls, with 60% of alcohol drunk as spirits, alcopops, and wine—a large increase since the mid-1990s when alcopops were created to encourage teenagers to drink spirits. Cirrhosis is now being diagnosed in some as early as the late teens.

Model of care

Provision of specialised services for liver disease, hepatobiliary surgery, and transplantation in children is centralised to the three national centres in London, Birmingham, and Leeds, which provide geographical equity and access for children from England, Scotland, Wales, and Northern Ireland. Experts on liver disease have a national consensus about the conditions that are managed in these centres, which were directly funded by the National Specialised Commissioning Group but are at present funded centrally as a Highly Specialised Service by the respective area team for NHS England. Each centre provides 24 h a day, 7 days a week access and support to referring hospitals within agreed referral pathways, and a shared care network with regional paediatric gastroenterology centres or district general hospitals to provide outreach and care near the patient's home.

This centralised model of care not only produces high-quality outcomes, but also is cost effective and serves as a benchmark for the international management of children with biliary atresia.[151] The British Association of Paediatric Surgeons have recommended that the operative management of primary liver tumours should be regarded by a multidisciplinary group at each of the three specialised centres so that resection or liver transplant are done by an expert team. All three centres have a large research infrastructure and provide a 3-year training programme for paediatricians to specialise in paediatric hepatology, the only accredited programme in the world. Similar accredited training is provided for trainees in paediatric liver surgery and for allied health professionals. These centres actively engage with parents and young people in defining the delivery of care for paediatric liver disease.

Early diagnosis of biliary atresia

A community based audit[152] estimated the incidence of neonatal liver disease at 1 in 1500 livebirths of which, biliary atresia is the commonest cause. Outcomes and survival of the child after surgical drainage procedures[150,151] is dependent on early diagnosis. Unfortunately, delayed recognition of jaundice in infants in primary care and late referral to a liver centre continue to be a major difficulty despite published guidelines.[153] In a retrospective analysis (Davenport M, UK Biliary Atresia Register, personal communication) of data from King's College Hospital, UK, 30 (10%) of 309 babies with biliary atresia born between 1999 and 2013 had surgical correction after 90 days of age, with a mortality of 14% (5 of 36) compared with 7·6% (21 of 273) in children who had their surgery before 90 days of age emphasising the need for early diagnosis. Screening for neonatal jaundice in Taiwan, by use of stool colour charts, effectively identified infants with biliary atresia and halved the number of mortalities by ensuring that surgery took place before the baby was aged 90 days.[154] In the UK, screening of bile acids in dried blood spots was not valuable,[155] but measurements of conjugated bilirubin (>20 μmol/L) in neonatal blood samples between 6 days and 10 days of age were a sensitive and specific marker of biliary atresia.[156] Technology needs to be developed for detection of conjugated bilirubin in dry blood spots. NICE guidelines[153] suggest that any infant who has jaundice for more than 14 days or has persistently pale stools should have their total and conjugated bilirubin measured; the British Society for Paediatric Gastroenterology and Hepatology guidelines[157] emphasise the necessity to investigate the presence of liver disease if the concentration of conjugated bilirubin is greater than 25 μmol/L.

Many genetic diseases in infants also benefit from early diagnosis and management. Advances in technology, notably new genetic sequencing or whole-exome sequencing, will soon become available to clinical practice thereby allowing specific and early diagnoses of paediatric genetic disorders, including progressive familial intra-hepatic cholestasis and Alagille's Syndrome, improving the management and outcomes of these diseases.[158]

An increased awareness for professionals and the public of the results of prolonged jaundice in the neonatal period would ensure prompt referral from primary or secondary care. Training of midwives, health visitors, GPs, and general paediatricians in the early recognition of infants with possible biliary atresia among the high volume of those with physiological jaundice, is essential if outcomes are to be further improved.

Prevention of chronic hepatitis from infection of hepatitis B and C

Chronic hepatitis B and C virus in childhood is mainly due to maternal transmission and accounts for a substantial burden of disease that often does not manifest until adulthood.[159,160] Although antenatal screening for hepatitis B and immunisation of the infants of mothers infected with the virus is mandatory, hepatitis C is not part of the antenatal programme except in populations perceived to be at high risk. Many children with hepatitis B or C virus are only diagnosed as a result of incidental findings or deranged liver enzymes. Preliminary data from Public Health England suggest that despite the mandatory programme, this immunisation is failing to be delivered by some public health services, which could lead to chronic infection of hepatitis B in missed children.[161] For example, no data were submitted from primary care trusts to verify that any child born in Birmingham from a mother infected with hepatitis B had received a complete course of the hepatitis B virus vaccination. Additional

measures to interrupt transmission in mothers who are highly viraemic with the use of nucleoside analogues tenofovir or entecavir should also be mandatory.[161]

Strategies need to be implemented to identify viral hepatitis C in pregnant mothers who could be treated post partum along with infants infected with the virus, by use of the new, highly effective and safe DAAs. In addition to universal immunisation programmes to prevent hepatitis B virus in childhood, these measures would have a substantial effect on public health on the future burden of liver disease in the country. Development of a safe and effective six-in-one vaccine for infants would help with the uptake of hepatitis B virus immunisation in practice.

Occurrence of non-alcoholic fatty liver disease

Childhood obesity in the UK has increased every year since the 1970s. Statistics from the National Child Measurement Programme for 2011–12 reported the prevalence of overweight children aged 3–4 years was 22·6% (with 9·4% classified as obese) and 33·4% in 10–11 year olds (19% obese).[162] Non-alcoholic fatty liver disease is just one of the potentially life limiting results of obesity and is now the most prevalent liver disorder in children and young adults in high-income countries with an overall prevalence of between 2·6% and 9·8% in people of who are overweight, rising to 42% to 77% in the obese.[163] The prevalence could be underestimated in view of the insidious onset of non-alcoholic fatty liver disease and the poor sensitivity of investigations.[164] Cirrhosis due to non-alcoholic fatty liver disease has been described in childhood with progression to end-stage liver disease, leading to death or liver transplantation.[165]

In addition to public health initiatives, namely increased physical activity and avoidance of high sugar and fat,[165] the school environment offers a unique opportunity to provide guidance and action as part of the educational journey. We strongly recommend that the Department of Education should support reductions in obesity by ensuring nutritional standards in schools, maximising compulsory physical education, and further developing the curriculum to support public health messages with opportunities for children to learn the skills needed for a healthy lifestyle.

Autoimmune liver disease in children older than 2 years

Reported prevalence of autoimmune liver disease seems to be increasing in childhood and adolescence (2–18 years) from between 0·5 per 100 000 to 20 per 100 000.[166] A substantial proportion of children present with non-specific symptoms or are asymptomatic and are diagnosed as a result of incidental detection of deranged serum aminotransferases. Referral to a paediatric hepatologist is essential for further investigation, early institution of treatment, and to exclude metabolic diseases, particularly Wilson's disease, which need a completely different management approach. Outcomes for appropriate and timely immunosuppressive treatment for autoimmune liver disease are rated as good, but at least 70% of patients will need active treatment into adulthood and 10% of children progressing to end-stage liver disease who therefore have an effect on the resources and infrastructure of adult liver and transplantation services.[167]

Importance of transition services: paediatric to adult liver care

Adolescence is a unique period in human development in which the young person needs to become self-reliant and separate from parental control. Physiological and psychosocial factors can affect an adolescent's approach to risk, self-esteem, and relationships all contributing to poor compliance to medical advice and treatment. Poor adherence to drug regimen is the commonest cause of graft loss and death after liver transplantation in this age group.[168] Additionally, adult services are not trained and do not have the resources to provide multidisciplinary care to this age group.[169] Establishment of well resourced and supported transition services for adolescents is urgently needed for these patients with all forms of liver disease, especially because the numbers of patients are increasing as a result of improved survival in the younger age groups (table 4).

The Department of Health recognised the importance of strengthening professional education and developing clear pathways for transitional care and have developed a generic framework,[170] and NICE are developing clinical guidelines for this topic. Ultimately, the aim of transition programmes should be to foster the development of personal skills to equip young people in managing their disorder in the adult care system. Unfortunately, as in many areas of new demand, implementation is slow.

The appendix shows comments from two young adults (aged 20 years and 25 years) about their experience of making the transition from paediatric care to adult care share their "daunting" feelings about change of care from familiar doctors, absence of emotional support and to be looked at as "just another patient".

See Online for appendix

Links between local paediatricians and support services

The active involvement of general paediatricians and paediatric gastroenterologists in the local management of patients, essential in long term care, is needed. Additionally important is the continued support for the hub (central point of reference; the UK's three specialist

	Number of patients
Transferred to adult services 2008–14	753
Attending paediatric services 2012–14	2640
11–15 years	1502
16–17 years	624
18–25 years	514

Table 4: **Number of people aged 11–25 years attending paediatric specialist liver services in England before and after transition**

***Panel 12*: Recommendations for the care of paediatric liver disease**

1 Jaundice in infants should be included in the parent held record (red book) and technology developed for detection of conjugated bilirubin (>25 μmol/L) in dry blood spots
2 Universal immunisation against hepatitis B once a six-in-one effective vaccine is available should be implemented and so should antenatal screening for hepatitis C, allowing for treatment of infected mothers and children after delivery
3 Public Health England should work with the Department of Education, primary care, and school health in the prevention of childhood obesity and to extend investment in the National Child Measurement Programme
4 Adult and paediatric providers should work together with an increased input from psychology services, social services, and the education sector in dealing with the transition period from child to adult care

centres) and spoke (channels for access and communication; the joint outreach clinics) approach around the three centres including joint outreach clinics across the UK. Both these recommendations need to be recognised to allow patients to be cared for close to their homes and in providing educational value for their local care team. The provision of support workers at paediatric outpatient clinics is important to provide emotional support and informed empowerment for children and their families (panel 12), together with partnership of the Children's Liver Disease Foundation that produce written information and educational events.

Economic analysis for the costs of liver disease and modelling of effects of scaling-up prevention and treatment services

Economic assessment

The economic costs of liver disease encompass the NHS spend, the cost to society (in terms of lost productive output), and the opportunity cost of failing to address and manage risk factors for advanced stages of this disorder.

On the basis of Hospital Episode Statistics, the costs of admissions and outpatient attendances for people with a primary diagnosis of liver disease were about £270 million in 2012–13 in secondary care alone (Longworth L, unpublished). In 2008, the latest breakdown of spending by the NHS by 57 categories of disease was published and included an analysis of the aggregated spending of English primary care trusts during 2006–07.[171] In 2007, the annual cost to the NHS from cirrhosis and liver cancer due to alcohol consumption in England was £566 million[172] and is rising by 10% per year.[173] At present in England, about 640 000 patients have been identified with liver disease. Between April, 2012, and March, 2013, 34 347 people were admitted to hospital with a primary diagnosis of liver disease[64] and around 266 125 outpatient attendances were reported (Longworth L, unpublished); liver disease cause by alcohol accounted for almost half these admissions (128 272 [48·2%]). Mortality of inpatients with liver disease is high at 3040 (8·8%) compared with in-patient mortality of 1·4% for all hospital stays in 2012, and was notably high across younger age groups—eg, age 30–49 years mortality was 7·2% and at ages 50–69 years was 9·2% (Longworth L, unpublished). A large UK population study[22] into survival in patients with cirrhosis reported low survival probabilities for patients admitted to hospital with a first diagnosis of cirrhosis compared with ambulatory patients. These results show that an early diagnosis and management of disease in a community or outpatient setting could reduce emergency admissions and improve patient survival, thus resulting in substantial cost savings.

Annual costs to health care in the USA are about US$22 752 for compensated cirrhosis and $59 995 for patients with end stage liver disease.[174] In 2006, annual health-care costs in the NHS for decompensated liver disease were estimated to be £9120.[175] 1334 admissions to hospital related to a primary diagnosis of alcoholic liver disease between April, 2012, and March, 2013, with a mean average length of a patients' stay of 11·5 days and an estimated total cost of £116 million. Despite a paucity of published data, the direct costs of liver disease to the NHS seem to be mainly in the hospital sector for patients with end-stage liver disease and poor outcomes.

Two of the main risk factors for liver disease in the UK, obesity and alcohol, generate greater health-care costs than do risks associated with liver disease alone. Alcohol was estimated to result in costs of £3·2 billion to the NHS in 2006–07 (through a calculation of the population attributable fractions that relate to alcohol as a risk factor for other conditions, such as seizures and accidents).[171] When costs to the criminal justice system, the economy, and social care were estimated by the UK Cabinet Office in 2003, the total cost of alcohol to society was about £20 billion.[176] A similar analysis in 2007 by the National Social Marketing Centre produced a much higher estimate of £55·1 billion, consisting of a £21 billion cost to individuals and families or households; £2·8 billion to the public health and health-care services; £2·1 billion to the criminal justice system, education, and social services; £7·3 billion to employers; and, £21·9 billion in human costs (reduced quality of life-adjusted years).[177]

Upscaling of treatments

Upscaling for alcohol interventions

Despite the government's alcohol strategy focusing on crime and social costs,[178] the charity Alcohol Concern estimates that only 5·6% of dependent or harmful

drinkers access available treatments every year. The charity emphasised that local primary care trusts spent an average of £600 000 a year on alcohol treatment and counselling services, representing just 0·1% of a typical annual expenditure by these trusts.[3] We have done economic analyses of many of our proposed recommendations to reduce alcohol consumption and the cost of associated disorders in the UK. For instance, a minimum pricing per unit of alcohol of 40 pence is estimated to generate a potential saving of £100 million resulting from positive effects on health, crime, and employee absenteeism.[179]

Screening and brief interventions identify people drinking at harmful levels and provide a structured way to deliver advice, help, and support. Evidence for the effectiveness of screening and brief interventions in reducing harmful drinking is good and strongest when delivered to individual people through primary care.[133,180,181] Cost effectiveness of screening and brief interventions in primary care in England has been modelled by use of two main scenarios: first, nurse-led screening and brief interventions in new registrations at a GP practice, and second, GP-led screening and brief interventions at the next consultation.[182] Different screening techniques were assessed under a range of assumptions in relation to effectiveness and cost during a period of 10 years. The next registration approach (nurse-led screening and brief interventions for all patients newly registered at a GP practice) had a smooth profile of screening volumes at an estimated cost of £10 million per year, but excluded 26 million people from screening during this timeframe. By contrast, the doctor led screening and brief intervention (next appointment model) screened 35 million people in the first year but also had a large proportion of the total £700 million cost in the first year. However, during 10 years only 1·5 million people would be left out of this screening programme. With the use of base-case assumptions in the next registration model, the £95 million cost of the programme was reported to be both cost-saving to the NHS and improved public health in accruing 32 000 quality-adjusted life-years (QALYS). Even with pessimistic assumptions of cost and effectiveness, screening and brief interventions were cost effective apart from scenarios where a GP was needed to give an intervention of 25 min. Likewise, switching to a next appointment compared with a next registration scenario substantially increased the costs but also the associated benefits. A consultation-based approach led by GPs to use screening (using the Fast Alcohol Screening Tool [FAST], a four-item initial screening test developed for busy clinical settings) would cost five times as much to deliver (£497 million), but would also deliver three times the downstream NHS savings (£682 million) from reduced admissions to hospitals and health-related quality of life (108 000 QALYs), than with present approach in practices. Such a policy needs large-scale implementation, with the supply of resources for primary care needs, but delivers interventions to almost 80% of hazardous and harmful drinkers during a 10 year period. Many aspects with respect to the effectiveness associated with different durations and delivery models for screening and brief interventions are unknown and NICE recommend the assessment of these in practice.[179]

Screening and brief interventions applied in hospitals can help harmful drinkers who have little contact with primary care. The Paddington Alcohol Test can be administered by accident and emergency staff to identify and advise those in need of onward referral to a nurse specialist. For every two patients accepting such an appointment, one patient does not re-attend during the next year.[183] Analysis of the Paddington Alcohol Test suggested that early identification of harmful or hazardous drinkers in an accident and emergency department is likely to be cost effective.[184] Hospital-based alcohol teams are also cost effective.[184] Nottingham Hospital's alcohol team led by nurses provides inpatient assessment, brief intervention, liaison with services for substance misuse, and access for alcohol detoxification for inpatient or outpatients on the hospital site. This service at Nottingham resulted in a reduced number of admissions for detoxification, reduced patients' length of stay, and reduced self-reported alcohol consumption compared with standard counselling by physicians. Additionally, the number of primary care consultations was reduced and a reported decrease in violent incidents in hospital where alcohol was a substantial factor. A similar team comprising of a psychiatry-based liaison nurse, a liver nurse practitioner, and consultants in psychiatry and gastroenterology was established at the Royal Bolton Hospital (Bolton, UK) and has saved more than 1000 bed days every year by reducing inpatient detoxifications.[185]

Upscaling for hepatitis C virus treatment

A dynamic model, previously mentioned, for the frequency of transmission and re-infection in people who continue to inject drugs, shows that present treatments available can not only cure many of those treated, but also importantly can reduce both onward transmission of infections of hepatitis C virus and thereby prevalence of hepatitis C virus in people who inject drugs by up to 75% in 15 years. This reduction was achieved with slight upscaling of present treatment to 98 of 1000 people who inject drugs annually.[105]

With the use of the new treatment regimens, it is suggested in a recently published model of optimum strategies for minimising the prevalence of hepatitis C viral infection in England, would result in a 95% reduction (from 144 000 to 6200) in the prevalence of hepatitis C viral infection, an 80% reduction in hepatocellular carcinoma, and 5200 deaths from liver disease caused by hepatitis C virus could be averted by 2030 (figure 16) by increasing diagnosis and number of people treated by 2·7 times from present figures.[186] The

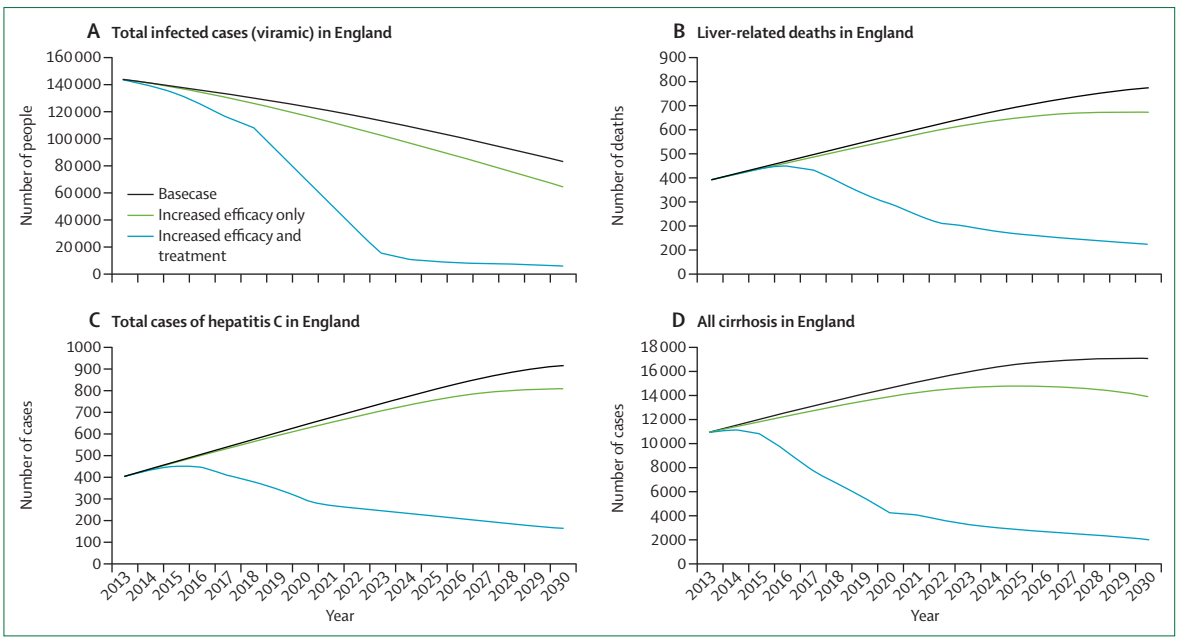

Figure 16: **Modelling of results of optimum strategies to minimise the present and future prevalence of infections from hepatitis C virus in England**
Data are from Wedemeyer and colleagues,[186] by permission of *Journal of Viral Hepatitis*.

	Base case	2014	2016	2018	2030
Eligibility	60%	60–80%	80%	95%	95%
Number of patients treated	5430	8150	11700	14700	600
Stage of disease treated	Any	≥F2	≥F1	Any	Any
Numbers newly diagnosed	5600	6700	10000	15100	880

F1–F4 are grades of liver fibrosis. F1=mild. F2=moderate. F3=bridging. F4=cirrhosis.

Table 5: **Optimum strategy to reduce the future burden of hepatitis C virus with liver disease**

optimum strategy requires the rapid use of new treatments and an increase in the number of patients treated from the present 5430 to 14700 in 2018 (table 5). To increase treatment numbers needs an active case finding strategy and broad eligibility for treatment to include the active treatment of patients such as injecting drug misusers who are infected with hepatitis C virus. In this model, new diagnoses need to rise from 5600 to about 15100 in 2018 (table 5) every year, for which a combination of public and professional education and ready access to testing services. Near-patient dried blood spot test and saliva testing is available to help achieve this target.[187,188] Upscaling of treatment for viral hepatitis C in this way could avoid costs of more than £900 million of health-care treatments related to dealing with cirrhosis complications, although detailed economic assessment is not possible until the costs of these new antiviral drug regimens are known.

Upscaling the use of non-invasive markers of liver fibrosis

Advances in non-invasive tests (NITs) of liver fibrosis have created new opportunities for the staging and monitoring of fibrosis and cirrhosis.[189] These tests are quicker, cheaper, and safer than a liver biopsy, but the tests have reduced sensitivity and specificity. Whether these tests are a cost-effective use of health-care resources depends on many factors, including accuracy of the tests, purpose of testing, effects of the diagnosis on the care pathway or behaviour, cause of liver disease, and health-care setting. A comprehensive systematic review and economic analysis[190] reported that some NITs are likely to be cost effective in specific settings.

In the upscaling of treatment for viral hepatitis C and the new diagnosis model previously mentioned, the greatest reduction in complications of liver disease and liver-related deaths was achieved by prioritising treatment initially for patients with moderate or advanced fibrosis.[186] In this context, the use of NITs to identify patients with the most immediate need for treatment could be useful and was recommended in WHO guidelines.[191] Similarly, in chronic hepatitis B virus infection, NITs are cost effective for showing the extent of fibrosis and for identifying specific groups of patients with moderate and severe forms of liver disease for treatment.[190]

The economic value for using NITs to determine the stage of alcoholic and non-alcoholic fatty liver disease is difficult to quantify owing to little robust data for the health outcomes and costs associated with effective treatments and the changes in patient behaviour as a result of diagnosis.[190–192] However, the availability of NITs opens new opportunities to use the tests in primary care settings. First, NITs could be used to better target the referral of patients with suspected fibrosis or cirrhosis to tertiary care. A model to analyse the use of NITs to refer only patients with a diagnosis of advanced fibrosis (or worse) to tertiary care, with patients diagnosed with no

fibrosis or mild fibrosis monitored in primary care, estimated possible cost savings of £317 per patient assessed.[190] However, this analysis should be viewed as exploratory because the evidence about the NITs is mainly derived from settings of tertiary care; further robust evidence for the cost and health consequences of alternative referral strategies are needed.[190] NITs could be used to extend testing to patients who are at risk of fibrosis through targeted screening programmes in primary care and thus help with the early diagnosis of fibrosis. Although some NITs have been developed with the intention of use in a primary care setting,[134] most have already been developed and tested in populations routinely seen in tertiary care settings. The potential roles of NITs when used in conjunction with new filters for the detection of liver fibrosis in primary care, such as the use of an ALT/AST ratio, could be of great value. Further research is urgently needed to establish the accuracy of NITs to be suitable for screening populations and to establish the success and cost-effectiveness in different screening approaches.

Upscaling of early life interventions to prevent liver disease

Drug misuse, obesity, and problematic consumption of alcohol have all been linked to community level factors, such as socioeconomic deprivation in childhood.[193,194] At an individual level, children who have had stressors or adverse childhood experiences, such as child abuse or poor quality family environments—eg, a household with domestic violence—have been associated with substance misuse and obesity later in life, and directly with liver disease in the USA.[195] A study of adverse childhood experiences identified strong associations between these events and health-harming behaviours to be linked with liver disease in the English population (figure 17).[76,196] Actions aimed directly at the prevention of obesity, drug misuse, and alcohol misuse in societies that ensure all communities have adequate services to support healthy development of children are likely to reduce subsequent uptake of health-harming behaviours, which are linked with liver disease (panel 13). Moreover, an evidence base of cost-effective measures that directly support parents and encourage bonding between parent and child are available and have been successful in reducing adverse childhood experiences.[197,198]

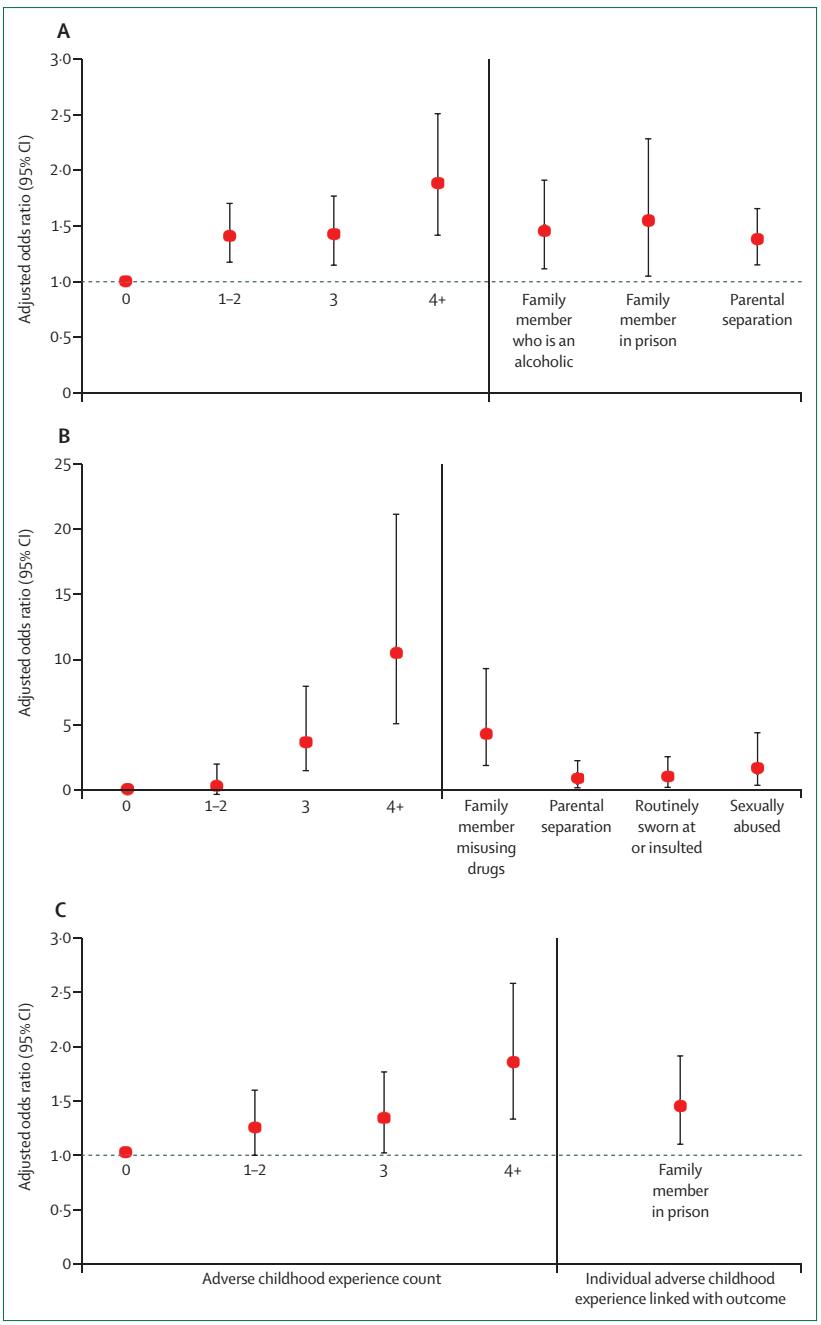

Figure 17: **Adverse childhood experience outcomes in relation to alcohol misuse, drug misuse, and poor diet**
Effects of (A) alcohol misuse (AUDIT score >5) (B) drug misuse (use of heroin or cracked cocaine), or (C) diet (≤1 portion of fruit or vegetables a day) on childhood experience. Data were used from Bellis and colleagues,[196] by permission of Oxford University Press.

New commissioning arrangements and the public interface

To address the high and increasing incidence of liver disorders in the UK, a range of activities is needed at different levels that require concerted action from national and local government, the NHS—starting with primary care—through to Public Health England, and from professional and patient organisations, all working in alliance. A result from the Health and Social Care Act of 2012, has been to make it difficult to create a national plan because of the philosophy that local commissioners are the people who know what is best needed for the populations that they serve. Furthermore, under the new system of the 2012 Health and Social Care Act, responsibilities for liver disease are split between the clinical commissioning groups, local area teams of NHS England, local authorities of Health and Wellbeing Boards, and Public Health England. Although the clinical commissioning groups will appoint secondary

***Panel 13:* Recommendations for upscaling of treatments**

1. Active case finding and increased treatment of viral hepatitis C to greatly reduce deaths from viral hepatitis C and its disease burden within a decade would be highly cost effective
2. An increased recognition of the value of interventions is needed to help to minimise adverse events in childhood to reduce the burden of liver disease later in life
3. Brief interventions for alcohol misuse in primary and secondary care are highly cost effective and should be widely promulgated
4. An urgent need to assess the cost effectiveness of non-invasive testing in a community setting to detect liver disease in need of onward referral or lifestyle modification alone

care for liver disease through the proposed acute hospital (liver unit) services, local area teams are likely to be responsible for this task, in whole or in part, for the specialist centres through the funding budget of separate specialist services. Difficulties from issues related to obesity and alcohol would both come within the remit of Public Health England and local authorities. The four Strategic Clinical Networks for addressing specific disorders of high priority do not include the liver and it is difficult to see how else strong coordinating action can be obtained. The National Hepatitis C Action Plan for Scotland has appropriate investment in infrastructure and target setting showing what can be achieved by a coordinated approach. Northern Ireland and Wales, similarly to Scotland, have Health Boards that are responsible for primary and secondary care and do not have a separation of purchaser and provider. The *Together for Health–Liver Disease Delivery Plan* for NHS Wales and its partners is too based on a coordinated approach between different groups to reduce infection rates for viral hepatitis B and C.

NHS England and Public Health England

The present Secretary of State for Health in the UK, Jeremy Hunt, has stated an ambition to improve the nation's cancer outcomes compared with other developed nations and is campaigning for the reduction of premature mortality. If this campaign were to include liver disease, as we recommended, this alone would encourage coordinated efforts in government departments and with the NHS for the prevention of liver disease. We believe that liver disease should be given a priority status because of its substantial effects on mortality in the working age population and because much of this disorder is preventable. The rising incidence of obesity, continued high quantities of alcohol consumption, and the largely hidden problem of chronic viral hepatitis represent major health threats for society. Enduring aspects of social inequality and geographical inequality (the so-called postcode lottery) in access to specialist services are associated with liver disease shows that this disorder should be of high priority.

Alignment of the activities by Public Health England and NHS England in reducing premature deaths from liver disease will be essential, but what unites the many bodies in the present health-care structure needs to work with the overarching indicators at the top of domain one in the NHS Outcomes Framework. Liver disease is specifically mentioned in improvement areas of this framework.

A clear link will need to be created through liver units at district general hospitals between commissioning of the recommended specialist centres and local services. Possible co-commissioning and a unified commissioning framework would help with efforts to tackle liver disease. For example, alcohol care teams are complex in nature and not easy to construct for the partnerships between mental health trusts and acute hospitals, and community teams and general practice. Public Health England seem to be already taking on the challenge of the obesity epidemic, which we suggest could easily be extended to become a national strategy for the other main issues for public health, including harmful drinking and viral hepatitis. An important step forward will come from Public Health England publishing and distributing liver disease profiles for local authority areas in England at the end of 2014. This analysis will provide great detail for liver disease in the UK and will be an important resource in bringing partners together to improve services and boost preventive measures. Development of these liver disease profiles into further sub-profiles for clinical commissioning groups and local authorities would be of value. A common dataset would help the different local bodies to work together to tackle liver disease, if action is to be effective. Additionally, identification and promulgation of examples of good practice promoted at local levels across the country would be a valuable part of a national campaign to address these major issues of public health.

Health and wellbeing boards and clinical commissioning groups

Because liver disease features prominently in both the NHS and Public Health Outcomes Frameworks, it should be a key component in the oversight and scrutiny of the Health and Wellbeing Boards of local authorities. Although the Joint Strategic Needs Assessment is a crucial framework for bringing together local partners in planning how to tackle liver disease in particular areas, an analysis from HCV Action[31] reported that liver disease does not feature on the agenda in many areas. Central government, Public Health England, patient groups, and professionals all need to be pushing for the presence of liver disease in local plans for health.

In the clinical commissioning groups an identifiable responsibility for liver disease and the development of

local strategies is needed. Not all clinical commissioning groups have developed plans for liver disease; however, feedback from local communities suggests that they are keen to engage in discussions about this agenda. NICE standards for recommended treatments should be provided for in the local care system. At present, there is widespread variation in the use of NICE guidelines; uptake and implementation should be mandatory in local care systems through community commissioning group contracts with health-care providers and monitored by the Care Quality Commission. An innovation in the northeast of the UK has seen the development of so-called care bundles that guarantee key interventions are completed for patients with decompensated cirrhosis. Such approaches ensure that evidence-based treatments are given early to patients and are a result of clinicians engaging with commissioners.

Inclusion of patients and web-based information portals

For an increase in the advocacy by patients for improvements to liver services, a minimum dataset of information needs to be available to them at a local level outlining disease profiles, waiting times, and clinical outcomes of interventions and treatments. Patients have a right to know what interventions and outcomes they should expect and guidance on what to ask, or do, if they are not receiving these. Additionally, patients should know how to access services that might not be locally available, including highly specialist services. People associated with the provision of local liver services need to have information about the extent of liver disease in their area, with an identified lead person and plan for service delivery. To further help with this access, we recommend that a new online webportal is created that includes information helpful to patients about the process of disease, treatment options, where services are available, expected standards of care, and information about diet and lifestyle. This portal could be connected to an existing health website, such as NHS Choices, with links to the patient groups and professional groups who support people with, and affected by, liver disease. A systematic collection of patient experiences is needed. A way in which patients might share their thoughts is by collating contributions to the website Patient Opinion pertaining to liver disease. Specialist societies—ie, the BSG and BASL—should have a key role in collating and contributing information to the proposed web portal. The important work of the British Liver Trust in disseminating knowledge of services and anticipated outcomes through locally organised patient support groups, needs to be strengthened.

Publication of outcomes and the national assurance system of accreditation

A minimum dataset for outcomes of liver disease needs to be completed and published for all NHS Hospital Trusts. At present, some hospital liver services do have outcomes that are available to consultants. With some manipulation, hospitals can extract data from the Patient Administration Systems, for example codes for the International Classification of Diseases, which across admissions could show the number of people who have been admitted, together with their discharge dates; data that should enable all hospitals to analyse admissions, mortality, and survival. We would like to see this system developed in hospitals across the country and for these findings to be made public and appropriate metrics used for local hospital and national datasets (panel 14).

At present, no national assurance system exists for liver services. Patient organisations and the specialist societies (the BSG and BASL) have a crucial role to work with Royal Colleges to develop accreditation systems that would help to assure that agreed standards are delivered in practice. The national project named Liver Quest (liver quality enhancement service tool) has already been started and, so far, 15 hospitals have signed up to be part of the accreditation scheme. To sign up to the scheme, hospitals have to complete a self-assessment against a developed framework, which comprises the identification of standards for care and the development of an information technology

For more on **Patient Opinion** see https://www.patientopinion.org.uk/

For more on **Liver Quest** see http://www.liverquest.org.uk/

***Panel 14*: Metrics for measurement of improvement in UK liver services**

A key aim of our Commission is to improve standardised liver cirrhosis mortality with a target of four of 100 000 population—equal to the best in Europe. Several other outcome and process metrics will be used to measure progress on an annual basis, including most importantly a new metric that will be the reporting of long-term survivals in cirrhosis and primary liver cancer using existing Office of National Statistics methods.[199]

National dataset

- Standardised liver mortality with years of life lost at aged 50 years, 65 years, and 75 years.
- Total number of patients with liver diseases admitted to hospital.
- In-hospital mortality for cirrhosis.
- 5 year and 10 year survival rates for cirrhosis and primary liver cancer.
- Viral hepatitis: admissions, mortality rates, long-term survival rates, number of patients given National Institute for Health and Care Excellence approved therapy for hepatitis B and C, together with percentage of viral clearance.
- Alcoholic liver disease: admissions, in-hospital mortality rates, long-term survival rates, and percentage figures for alcohol intake assessed in primary care.
- Obesity and related liver disease: Health Survey for England prevalence and trends.

Local hospital dataset

- Percentage of liver readmissions within 30 days after being discharged from hospital.
- Comparative mortality and survival rates.
- Percentage of variceal bleeds endoscoped within 24 h of admission.
- Number of referrals for transjugular intrahepatic portosystemic shunt procedure.
- Percentage of alcohol intake assessed during admissions and % brief interventions.
- Percentage of liver cancer cases reviewed at multidiscipline team meetings.
- Percentage of liver admissions reviewed by a hepatologist in 24 h, 48 h, and 72 h of hospital admission.
- Percentage of completion of care bundle for decompensated liver disease.

Panel 15: **Recommendations for new arrangements of commissioning**

1 National government together with the National Health Service (NHS) for England and Public Health England should ensure implementation of the domain one plan about reducing premature deaths from liver disease, in accordance with the campaign by the UK Secretary of State
2 The burden of liver disease should be included in priority areas for commissioning both by local services and through regional specialist services
3 An independent and objective online information portal should be established and contain data of services, standards of care, outcomes, and points of contact, which will help in promotion of the public's better understanding of liver issues and improve professional and patient advocacy
4 The government, through NHS England and Public Health England, should support Liver Quest in the accreditation of hospital services, the fledgling scheme for accreditation of hospital services
5 A new organisation (that we have called Liver Focus) should be created with the direction of the British Association For The Study Of The Liver and the British Society of Gastroenterology to provide leadership in liver disease and ensure implementation of reforms set out in this Commission.

platform to record outcomes in four areas: clinical quality; patient experience; integrated care; and leadership, workforce, and training of staff. A website has been developed to support units joining this scheme. Data from Liver Quest should be included on the national web portal for liver information as the project develops.

Formation of Liver Focus

To pursue our recommendations in this Commission and those from other major public bodies, including the All Party Parliamentary Groups, for implementing changes to care, an organisation needs to be set up to bring together the professional and patient groups to work on their shared interest in liver disease. Our proposed name for this new body, Liver Focus, emphasises its main purpose. The two national societies (BASL and BSG) would be the lead organisations in developing this body with various stakeholders. Liver Focus would have an appropriate infrastructure, a dedicated secretariat, an independent chair to represent patients, and vice-chairs to represent health professionals.

A human, social, and financial imperative shows the need to act now if the burden of liver disease and all its consequences are to be tackled, and if the health-care system is not to be overwhelmed by the cost of treating advanced stages of liver disease. Effective action will need reinforcement from various people from the Secretary of State, to NHS England and Public Health England, to local authorities and local NHS commissioning groups (panel 15). Our proposed organisation, Liver Focus, would bring together professional and patient groups and have an important role in maintaining the momentum for the coordination of effective action against liver disease.

Overall conclusions and key recommendations

In the UK, the present numbers of premature mortality and overall poor standards of care being afforded to patients with liver disorders are unacceptable.

Our ten key recommendations represent the most important of each listed in this Commission. We believe that these ten recommendations will have the greatest effect on reducing the burden of liver disease in the UK and should be given the greatest priority in implementation.

1 Strengthening of detection of liver disease at early stages and its treatment in primary care

Putting this recommendation first represents its importance we have accorded to it. Early detection of liver disease will thereby prevent the development of more serious illness through appropriate treatment.

Key parts to this recommendation include the positioning of liver disease in the so-called Big Five major chronic, preventable, and lifestyle-related diseases of cardiovascular disorders, diabetes, chronic lung disease, and renal disease, to maximise the effect from generic lifestyle interventions and chronic disease management. Second, for GPs to use a new management pathway for this disease, which includes the additional provision of the AST/ALT ratio in results from tests of liver function to help with the triage of substantial liver disease, thus avoiding unnecessary referrals of minor abnormalities to hospitals. Finally, for the inclusion of liver elastography as the preferred confirmatory test for detection of substantial hepatic fibrosis.

2 Improvement of support services for screening of patients at high risk in the community

Patients need to be able to access more of their care at local services. Key to this recommendation is the establishment of community hepatology posts for GPs who have had extra training and experience in liver disorders and could work closely together with consultants from the district general hospitals undertaking community-based sessions. Such people would have an important role in area health teams, organising the range of appropriate information flow about liver disease to clinical commissioning groups responsible for commissioning the range of required liver services in liver units of district general hospitals, including primary care and specialist services.

3 Establishment of liver units in district general hospitals and regional specialist centres to improve care for patients who are acutely sick

This recommendation is based on an enhanced 7 day acute service in the liver units of UK district general hospitals, together with an increased number of regional specialist centres distributed equitably around the country including critical care, treatment of hepatocellular cancer, high-cost virological services, hepatopancreaticobiliary surgery, and transplantation in

some centres. Accreditation of services would be through the programme of Liver Quest, which is promoted by the Royal College of Physicians (London,UK) and is already in clinical trial.

A multidisciplinary alcohol team led consultant, centred around patient care, and available 7 days a week should be mandatory in every hospital. This team should comprise of an alcohol specialist nurse and liaison psychiatry with outreach teams and close links to primary care and community alcohol services.

Goal-directed so-called care bundles for the management of cirrhosis and its associated complications and the screening of patients with cirrhosis for primary hepatocellular carcinoma should be the standard in every hospital and should qualify for a quality and innovation Commissioning for Quality and Innovation payment.

4 A national review of liver transplantation services in the UK

This recommendation addresses the urgent need to ensure an adequate capacity for use of the increasing number of donor organs that are available, with donations projected to increase by 50% by 2020. Our proposed national review would judge whether the established six centres have sufficient capacity for this future increase and the associated costs. The review should address too the present inequitable distribution of transplant centres in England because patients who live quite close to a transplant centre have a greater opportunity of receiving a transplant than do those who live some distance away.

5 Strengthening of the continuity of transitional care from child services to adult services

An increasing number of infants with surgically corrected biliary atresia and children who have received transplants are now living to adolescence and adulthood. Their care in childhood has not been matched by the development of appropriate transitional facilities for them in the adult sector. This recommendation calls on adult and paediatric providers of specialist liver services to work together, along with psychological services, social services, and education to deal with the transition.

6 Scaling-up of national action to reduce the UK's overall consumption of alcohol

Decreases in alcohol consumption is crucial if the figure for premature mortality from liver disease and the enormous burden on the health service from alcohol-related diseases, are to be reduced. Our evidence-based proposals are in agreement with recommendations from various professional and expert bodies, including the All Party Parliamentary Group on liver disease and the All Party Parliamentary Group on alcohol misuse, and the independent group of experts led by the Alcohol Alliance and the University of Stirling who, in 2013, produced *Health First: an evidence based alcohol strategy for the UK*.[49] Of the ten specific recommendations stated by Health First (panel 7),[49] the following six are most relevant to reducing the overall consumption of alcohol in the UK. First, a minimum price of at least 50 pence per unit of alcohol should be introduced for all alcohol sales together with a mechanism to regularly review and revise this price. Second, tax on alcohol products should be proportionate to the volume of alcohol contained to incentivise the sale of low-strength products. Third, at least a third of every label on alcohol products should be used to state evidence-based health warnings as specified by an independent regulatory body. Fourth, sales of alcohol in shops should be restricted to specific times of the day and designated areas. Fifth, licensing legislation should be comprehensively reviewed so that licensing authorities are empowered to tackle alcohol-related harm by better control of their jurisdiction. Sixth, advertising and sponsorship of alcohol should be restricted and subject to independent review with a limitation for advertising to factual information about brand, provenance, and product strength. An independent body should be established to regulate promotion of alcohol, including product and packaging design.

7 Promotion of healthy lifestyles to address the present epidemic of obesity

25% of the UK population are obese and 70–90% of patients who are obese have non-alcoholic fatty liver disease. The obesogenic environment urgently needs to be reduced through local or national measures to promote healthy lifestyles, along with new government legislation, including taxation of foods with a high sugar content and sweetened drinks. Voluntary measures in the food retail industry are unlikely to have a sufficient effect on obesity. For patients who are obese, the AST/ALT ratio should be an addition to liver function tests to triage the patients with non-fatty alcohol liver disease who are most likely to develop fibrosis, cirrhosis, or hepatocellular cancer. Other parts of the recommendations relate to establishment of metabolic clinics in every major hospital to manage disease consequences of severe obesity, including bariatric surgery. For children and adolescents, an integrated approach is needed between Public Health England, the Department of Education (UK), and school health to promote healthy eating and a non-sedentary lifestyle.

8 Eradication of infections of hepatitis C virus by 2030 and reduction in disease burden from heptatitis B virus

Ambitious targets should be set at local and national levels to now eradicate viral hepatitis C with the use of new and highly effective antiviral drugs, which are being licensed. To target the large number of unidentified patients infected with hepatitis B or C virus, screening programmes will be essential particularly in urban areas and up-scaling of access to new drugs for patients infected with viral hepatitis C. For eradication of hepatitis B virus, identification of infection in immigrants coming into the

country from areas with a high prevalence, screening is essential as is access to long-term treatment with the effective antiviral drugs available. The universal infant vaccination programme against hepatitis B virus has been shown to be cost effective in other European countries with a similar prevalence and immigrant population. Failure to implement this immunisation strategy and monitoring of mothers infected with hepatitis B virus and babies born to them, should be regarded as a serious failure in care.

9 Increase in the provision of medical and nursing training in hepatology and wider opportunities for all health professionals to increase their knowledge of liver disease

An increase in numbers of training positions in hepatology is essential to rectify the low number of posts for consultant hepatologists as identified in this Commission and the NCEPOD report.[2] Core training for specialist registrars should be formalised to allow a final year of specialist training for district hospital consultants and for a final 2 years for consultants aiming to work in specialist centres. For specialist nurses, the development of robust educational links with university accreditation to masters level is needed. For the new community hepatologist positions, additional training in hepatology needs to be provided in conjunction with the Royal College of General Practitioners and Royal College of Physicians. Social services workers and other health professionals associated with the community services should, as we recommended, receive training in use of short interventions for patients who drink excessively and training in the most effective dietary and other measures for reducing a patient's bodyweight.

10 Launch of a national campaign to increase awareness of liver disease in the general population

A national campaign would aim to remedy the present poor knowledge of the general public about liver disease and its effects on health in the short term and long term. This campaign would emphasise the serious nature of liver disorders related to lifestyle and have added value by helping to correct the apparent stigma attached to liver disease that does not apply to other largely lifestyle-related disorders, such as those due to smoking and which can be classed in non-lifestyle related liver diseases. Along with a national campaign, we recommend that the NHS and Public Health England develop a priority plan for liver services to aid, particularly, in the commissioning of local services by the clinical commissioning groups and area health teams to ensure that the various advisory groups involved with commissioning bodies are properly informed.

Contributors

The first draft of this report was written by a core writing team led by RW. All authors contributed to the Commission's structure and concepts. The Commission was prepared under the general direction of RW. Data gathering was done by a supporting research team listed in the acknowledgments. The views expressed herein are those of the authors and they do not necessarily represent the views of any of the organisations involved in this report.

Declaration of interests

No commissioners were compensated for their time. We declare no competing interests.

Acknowledgments

We thank the following organisations who have offered invaluable assistance to the authors of this Commission: the British Association for Study of the Liver (BASL); the British Society of Gastroenterology (BSG); the British Liver Trust (BLT); the Foundation for Liver Research (FLR); the Royal College of General Practitioners (RCGP); and the Children's Liver Disease Foundation (CLDF). We thank the following people who shared data and the lead writers who largely contributed to the report and in particular to Natalie Day for transcribing the proceedings of meetings and in preparation of the report. Valuable discussions, advice, and research were provided by David Breen (University Hospital Southampton, UK), Iain Brew (HMP Leeds, UK), Liz Farrington (Royal Cornwall Hospital, UK), Jeff French (Strategic Social Marketing, UK), Michael Glynn (National Clinical Director for GI and Liver Diseases, UK), David Goldberg (Health Protection Scotland, UK), Charles Gore (Hepatitis C Trust, UK), Emma Greatorex (University Hospital Southampton Trust, UK), Ashley Guthrie (St James's Hospital Leeds, UK; British Society of Gastrointestinal and Abdominal Radiology, UK), Sharon Hutchinson (Glasgow Caledonian University, Glasgow, UK), Patricia McLean (Leeds General Infirmary, UK), Mike Moore (University of Southampton, UK), Graeme Poston (NHS Specialised Commissioning HPB Clinical Reference Group, UK), Mary Ramsay (Public Health England, UK), Jacqueline Swabe (GI Pharmacy, University Hospital Southampton, UK), Alison Taylor (Children's Liver Disease Foundation, UK), Mark Thursz (Imperial College London, UK), Julia Verne (Public Health England, UK), John Wass (Royal College of Physicians, UK), and Andrew Yeoman (Aneurin Bevan University Health Board, UK).

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