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Liver cirrhosis in England-an observational study. Are we measuring its burden correctly?

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Abbreviations: ONS-Office for National Statistics; ICD10-International Classification of Disease 10th version

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Abstract

Objectives: Mortality due to liver disease (of which cirrhosis is the end-stage) is increasing more than any other chronic condition in the UK. This study aims to demonstrate that (i) exclusive reliance on mortality rates may not reveal the true burden of liver cirrhosis, and (ii) diverse use of diagnostic coding may produce misleading estimates.

Design: Observational study

Setting: The Office for National Statistics death registry was interrogated to investigate liver cirrhosis mortality trends in England and Wales, from 1968 to 2011.

Main outcome: Poisson regression was used to examine standardised mortality trends according to three different definitions of liver cirrhosis based on the specificity of diagnostic codes: 1(chronic liver diseases), 2 (alcoholic and unspecified cirrhosis only) and 3 (cirrhosis as end-stage liver disease). The mortality trends were compared to incidence rates established in a previous population-based study (based on definition 3), from 1998 to 2009, to investigate discrepancies between these two measures.

Results: Over the study period, the overall standardised liver cirrhosis mortality rates were 8·8, 5·1 and 5·4 per 100,000 person-years for definitions 1, 2 and 3 of respectively. The mortality rates for definition 3 in 1998 and 2009 were 6·2 and 5·9 per 100,000 person-years respectively; whilst the equivalent incidence rates were at least three- and six-fold higher: 23·4 and 35·9 per 100,000 person-years respectively. This discrepancy between incidence and mortality rates was also at least three-fold in men and women separately, and across age-groups.

Conclusion: Liver cirrhosis mortality rates varied greatly by definition of disease. Additionally, mortality rates underestimated the incidence of liver cirrhosis by at least three-fold between 1998 and 2009. Mortality data should not be used exclusively as an indicator for the burden of liver cirrhosis in the population. Routinely collected healthcare data are available to measure occurrence of this disease.

Key words: Liver cirrhosis, Mortality, Incidence, Routine data

Article summary

Strengths and limitations of this study

- First study to quantify the difference in liver cirrhosis mortality rates based on different definitions of disease.
- First study to demonstrate that overall mortality rates underestimate the incidence of liver cirrhosis by at least three-fold.
- A key strength of the study is the large number of registered deaths and the long period of time that the data were obtained over.
- A potential limitation of death registry data is the change in coding practice over time.
- The Office for National Statistics data cover deaths in England and Wales combined whereas the incidence data are based solely on English general practices.

INTRODUCTION

Liver disease, of which liver cirrhosis is the end-stage, constitutes the third commonest cause of premature death in the UK.[1] According to the UK's current Chief Medical Officer (CMO), the rate of increase in premature mortality from liver disease and from cirrhosis is substantially higher in the UK than other countries in Western Europe.[2] Further, cirrhosis per se has recently been reported to be increasing in the UK at a faster rate than the top four most-commonly diagnosed cancers (lung, breast, bowel and prostate).[3] The main reasons for the rise in cirrhosis are probably parallel increases in alcohol consumption and obesity.[1,4] In the UK, alcohol consumption per person across the population has more than doubled in the last half-century and one in four adults are now considered to be obese.[5,6] These are preventable causes and interventions such as minimum pricing for alcoholic drinks and campaigns for healthier lifestyles have been considered as part of a strategy to reduce liver disease.[7,8]

Despite its 5-year mortality being equivalent to that seen in colon cancer, and in contrast to the monitoring of new cancer diagnoses, there is no mandatory registration of cirrhosis cases in the UK or elsewhere in the world.[9] Estimates of the occurrence of cirrhosis, and consequently the assessment of success or failure of primary interventions, have therefore been primarily drawn from death registry data.[1,2] This methodology is likely to mask the true incidence of cirrhosis. Firstly, not everyone with cirrhosis dies directly due to the disease and our recent population-based study estimated that only 32% of deaths in people with cirrhosis had a cirrhosis related code anywhere on their death certificate.[10] Secondly, there is a time-lag between diagnosis and death. Hospital-based studies have reported survival estimates at 1-year of around 65%.[11,12] Those who do not die immediately after diagnosis, and those who do not die directly from the disease, will not be accounted for by reliance on the death registry.

Establishing accurate estimates of cirrhosis is further compounded by the fact that there is no clear boundary between liver disease and cirrhosis. There are a myriad of liver diseases and for each one patients progress to cirrhosis at different rates, if at all.[13] Previous authors of well cited papers have used a range of codes representing different liver diseases when reporting mortality due to "liver cirrhosis".[11,12,14] Subsequently it is often not possible to determine whether authors are truly examining liver disease or cirrhosis per se. Given the dependence of health service planning on accurate knowledge of occurrence of disease, we sought to use routinely available data to (i) examine how cirrhosis mortality rates may differ according to the range of specificity of diagnostic codes used within the hepatology community; and (ii) quantify the difference between cirrhosis mortality rates (from death registry data) and cirrhosis incidence rates (from linked routine healthcare databases) based on the same definition of disease and over the same time period.

METHODS

Data sources

We obtained mortality data from the Office for National Statistics (ONS) website (www.ons.gov.uk). These data are derived from registered death certificates and consist of counts of death by underlying cause (based on the International Classification of Disease (ICD)[15]) year of death, 5-year age-group, and sex for England and Wales from 1968 to 2011. Population data for the respective years were also obtained from the ONS website stratified by 5-year age-group and sex. We used the linked Clinical Practice Research Datalink (CPRD) and English Hospital Episodes Statistics (HES) to conduct a cohort study identify incident diagnoses of cirrhosis between 1998 and 2009. The diagnoses in the CPRD are made by histological examination and/or characteristic clinical signs of advanced liver disease.[3]

Definitions of cirrhosis

We used three definitions of cirrhosis according to the specificity of ICD diagnostic coding:

Definition 1: This code list was developed by Leon et al.[14] and has been selected as it is a relatively broad definition of cirrhosis and includes other chronic liver disease (e.g. alcoholic liver disease and chronic hepatitis), and has been used widely by other authors.[16]

Definition 2: This is a restrictive definition used by Jepsen et al.[17], including only alcoholic and unspecified cirrhosis of the liver.

Definition 3: This code list reflects cirrhosis as the end-stage of liver disease and includes codes for portal hypertension and oesophageal varices which are not included in the above definitions. This code list is the same definition our group has used previously to define a cohort of people with an incident diagnosis of cirrhosis in England using the linked CPRD and HES.[3]

To provide a context, we combined all liver diseases according to ICD version 10 chapter 'Diseases of the Liver' (K70-K77) and refer to this this category as 'Liver disease'. During the calendar period considered three different revisions of the ICD were used and mapping across these 3 versions are shown in Supplementary Tables 1 and 2.[15,18,19]

Statistical analysis

Mortality rates

Age at death was categorized from the age of 15 years in three groups (<45, 45-64 and ≥65 years). We determined crude mortality rates per 100,000 person-years from 1968 to 2011, for liver disease and all three definitions of cirrhosis. We calculated age- and sex-stratum specific cirrhosis mortality rates and applied these to the 2011 population to generate annual standardised mortality rates. Poisson regression modelling was used to estimate mortality rate ratios with adjustment for age and sex. We determined average annual increase.

Incidence rates

Determining the incidence of cirrhosis (using definition 3) has been described elsewhere.[3] In brief, we defined a cohort of incident diagnoses from the linked CPRD and English HES data from 1998 to 2009 for adults from the age of 18 years onwards. Estimates of incidence from the study have been standardised to the 2011 population and used in this current paper to make a direct comparison with standardised mortality rates over the same time period and using the same definition of disease.

RESULTS

Standardised mortality rates

The overall standardised mortality rates for definitions 1 to 3 of cirrhosis over the study period were 8.8 (95% CI 8·8, 8·8), 5.4 (95% CI 5·4, 5·5) and 5.1 (95% CI 5·0, 5·1) per 100,000 person-years, respectively. Figure 1 displays the standardised mortality trends from 1968 to 2011 for all definitions. There was only a marginal difference in absolute and relative terms between liver diseases combined and definition 1, and similarly only a marginal difference between definitions 2 and 3.

Between 1979 (the introduction of ICD-9) and 2001 (the introduction of ICD-10), the average annual relative increase in mortality from cirrhosis was 3.8 (95% CI 3.7, 3.9), 1.3 (95%CI 1.3, 1.4) and 1.4 (95% CI 1.2, 1.5) for definitions 1, 2 and 3 respectively. From 2001 onwards the increase was smaller for all definitions: 0.7 (95%CI 0.5, 1), 0.3 (95%CI 0.3, 0.4) and -0.3 (95%CI -0.6, -0.04) respectively.

From 1992 to 2008, the absolute difference in rates between those of definition 1 and definition 2 diverged further with time. For example, the absolute rates for definition 1 in 1992, 1996 and 2008 were 7·8, 9·4 and 14·6 per 100,000 person-years; the equivalent for definitions 2 and 3 were 4.8, 5.5 and 5.8, and 5·5, 5·7 and 5·8 respectively.

Change in cause of death over time

In order to explore possible reasons for the divergence in deaths between the different definitions of disease, from 1992 and 2008, we have presented the distribution of causes of death in 1992 and 2008 per definition (Table 1). We have not displayed the distribution for definition 2 as it is similar to that of definition 3.

In 1992, the percentage of deaths attributed to alcoholic liver damage (ICD-9 5713), which is included in definition 1 but not in definition 3, was 21·2%. This increased to 40.1% in 2008 (ICD-10 K70.9). During the same time frame, the percentage of deaths due to alcoholic cirrhosis (ICD-9 5712) decreased from 24·6% to 15·7%. In contrast, the distribution of causes of death of definition 3 did not change that dramatically. For example, 35·4% of deaths in 1992 were due to alcoholic cirrhosis of the liver (ICD-9 5712) and the equivalent proportion in 2008 was 39·4% (ICD-10 K70.3). Similarly, the proportion of deaths due to cirrhosis without mention of alcohol was 52·2% in 1992 (ICD-9 5715) and 57·5% in 2008 (ICD-10 K74.6).

Comparison between mortality and incidence rates

In a previous study we determined the incidence of cirrhosis in England during the period 1998 to 2009 using definition 3 of cirrhosis.[3] These rates have been standardised to the 2011 population and inserted into Figure 1. Specifically, the standardised incidence rates were 23·4 and 35·9 per 100,000 person-years in 1998 and 2009 respectively. This is in sharp contrast to the standardised mortality rates of 6·2 and 5·9 per 100,000 person-years in 1998 and 2009 respectively (in England and Wales). The overall rate of change between 1998 and 2009 was 50.6% for incidence, whereas mortality rates decreased by 2·5% over the same time period. The mortality rates according to definition 1 were also substantially less than the estimates of incidence; 11·1 and 13·8 per 100,000 person-years in 1998 and 2009 respectively, equating to a rate of change of only 28·9% across the period (Figure 1).

For both sexes, the standardised incidence rates were between 3- and 6-fold that of mortality (definition 3), in all age-groups, across the study period (Figures 2 and 3). The incidence rates were also substantially higher than mortality rates based on definition 1, for both men and women and across all age-groups.

DISCUSSION

Main findings

We found that both the absolute and relative cirrhosis mortality rates varied with differing disease definition. The overall age-standardised mortality rates during 1968 to 2011 were 8·8, 5·1 and 5·4 per 100,000 person-years for definitions 1 to 3 respectively. Careful consideration should be taken when selecting diagnostic codes for cirrhosis so that they are in line with the research question and research wastage is minimised. Further, using different routinely available clinical datasets we have previously demonstrated that between 1998 and 2009 the incidence of cirrhosis increased by 50·6% which is in contrast to a decrease in mortality from cirrhosis of 2·5% based on the same definition of disease.[3] Cirrhosis incidence rates were consistently higher than mortality rates, at least three-fold between 1998 and 2009, independent of age and sex. Mortality rates should therefore not be used alone to monitor the occurrence of cirrhosis; alternative sources of routinely collected data should be considered.

Strengths and limitations

This is the first study to quantify the difference in cirrhosis mortality rates by differing definitions of disease and the first to compare cirrhosis mortality and incidence rates using the same definition of disease. Key strengths of the study are its external validity, the large number of registered deaths, and the long period of time that the data were obtained over. The latter meant that we were able to report trends of mortality rates for a period of more than forty years. A potential limitation of death registry data is the change in coding practice over time, known as coding phenomenon. The change in rate of specific causes of death over time could be due to the use of different ICD versions throughout the study period rather than a true change. For example, the sharp increase in the number of liver disease deaths (definition) 1, after 1979, when ICD-9 came into use; followed by a

reduction in the rate of change from 2001 onwards when ICD-10 came into place. This phenomenon has been reported by others.[20] Coding phenomenon also occurs when doctors change the way they select codes on death certificates. For example, over time doctors may be more likely to use codes for alcoholic liver disease even in the presence of alcoholic cirrhosis. This may explain the increase in deaths coded as alcoholic liver damage in contrast to the fall in deaths coded for alcoholic cirrhosis, which we report in this study. Despite the potential changes in coding practice over time, mortality rates using the broadest definition of liver disease are still dramatically lower than the incidence rates of cirrhosis reported using a relatively restricted definition. Finally, the ONS data cover deaths in England and Wales combined whereas the incidence data are based solely on English general practices so we are not exactly comparing like with like. However, given similar liver disease mortality in England and Wales,[21] if death registry data for England only were available and had been used the discrepancy between mortality and incidence would highly unlikely be less than that which we report and our conclusions would remain the same.

Implications

Our findings provide evidence that using mortality data alone to measure the occurrence of cirrhosis could have major implications on healthcare planning. Given the sharp rise in cirrhosis incidence in the last decade that is not visible from mortality statistics, the NHS may well be under resourced and unable to cope with future demand on hepatology clinics. Mortality and incidence are two very different measures of disease burden. If only cirrhosis which leads to death from cirrhosis is of importance to clinicians and policy makers then measuring mortality is indeed the more appropriate measure. However if we are truly concerned with measuring the occurrence of cirrhosis and/or the impact of public health intervention strategies then incidence rates are crucial. When establishing the success of public health interventions aimed at reducing new disease, such as alcohol policies and healthy eating campaigns it is essential to set targets for incidence to determine if these sorts of

interventions have been effective or not. Evaluation of such interventions needs to account for the long sojourn between disease onset and fibrosis/cirrhosis, which can take between 10 and 30 years.[22] Mortality is even further away therefore even less relevant a measure than incidence. The study by Leon et al.[14] (definition 1) used mortality rates as they were believed to be important indicators of population levels of alcohol harm. However, our findings suggest that the use of incidence rates would have been more indicative. One recommendation for future work, from this study, is to measure the incidence of cirrhosis by using routinely collected healthcare data often known as 'Big Data'. Such data are becoming increasingly familiar and accepted in hepatology with, for example, the recent Lancet Commission recommending non-alcoholic fatty liver disease prevalence be measured by establishing a cohort from primary care data.[1] The strengths of using routinely collected data are from methodological and cost-effectiveness perspectives. Firstly, the recent linkage of primary care and secondary care allows a representative cohort of patients covering the full spectrum of disease to be identified, representative of the English population.[3,23] Secondly, accessing large amounts of routinely collected data for chronic diseases is substantially cheaper than establishing a bespoke prospective cohort of patients and following them potentially for several decades. Similar discrepancies between mortality and incidence figures have been shown in other diseases for which there is no mandatory recording such as idiopathic pulmonary fibrosis.[24] Routinely collected data may be appropriate to measure the incidence of this condition too.

The second implication of our findings is the necessity of careful consideration of disease definition. We have shown that the inclusion of patients who died from chronic liver diseases introduced an overestimate of cirrhosis mortality rates, by about 60%, comparing definitions 1 and 3 (8·8 per 100,000 vs. 5·4, respectively). Definition 1 included codes related to alcoholic liver disease such as alcoholic fatty liver disease (K70.0) and alcohol liver disease (K70.9), as well as autoimmune diseases. With respect to alcoholic liver disease, some patients with this condition can fluctuate

between alcoholic fatty liver and alcoholic hepatitis and not actually completely progress to cirrhosis, and if they stop drinking the architecture of their liver may return to normal.[13] Consequently, on one hand, it may be misleading to include codes such as alcoholic fatty liver disease (K70.0), alcoholic hepatitis (K70.1) and alcohol liver disease (K70.9) when intending to measure deaths due to cirrhosis. Conversely, one could argue that as these diagnostic codes represent diseases which could be a pre-cursor to cirrhosis they could actually reflect a poor specification of decompensated disease and hence cirrhosis. For example, this current study has shown that a particular difference between definitions 1 and 3 in the rate of change cirrhosis between 1992 and 2008 may have been mediated through an increase in deaths coded as the broader term "alcoholic liver disease" with a concomitant decline in the number of deaths coded as the more specific "alcoholic cirrhosis". One cannot disprove the possibility of an artefactual difference due to clinicians' certification practice rather than a true increase in alcoholic liver disease compared to alcoholic cirrhosis. Therefore, it may indeed be appropriate to use broader codes like alcoholic liver disease in order to capture patients with cirrhosis who may not have been certified as dying from cirrhosis per se. The key point is that code lists should reflect the precise research question that is being posed, otherwise results are misleading. Future research should take this finding into account.

Conclusion

This study has highlighted that reliance on mortality data alone may lead to an underestimate of the occurrence of cirrhosis, and indeed liver disease in general. Consequently the occurrence of liver disease in England is likely to be considerably worse than that which others report, including the current UK CMO.[1,2,25,26] Alternative sources of routinely collected data should be considered as a matter of urgency and appropriate definitions of disease employed. Accurate monitoring of the incidence of cirrhosis will allow the optimisation of limited healthcare services and provide

appropriate baseline figures from which to evaluate intervention, particularly those implemented at population level.

References

[1] Williams R, Aspinall R, Bellis M *et al*. 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. *Lancet* 2014;**384**:1953–1997.

[2] CMO report 2012 [Internet]. Available at https://www.gov.uk/government/publications/cmo-annual-report-2011-volume-one [last accessed 6th February 2016].

[3] Ratib S, West J, Crooks CJ *et al*. Diagnosis of Liver Cirrhosis in England, a Cohort Study, 1998-2009: A Comparison With Cancer. *Am J Gastroenterol* 2014;**109**:190–198.

[4] von Wulffen, M, Clark PJ, Macdonald GA *et al.* Liver-related mortality in countries of the developed world: an ecological study approach to explain the variability. Alimentary Pharmacology & Therapeutics 2016; **44**(1): 68-77.

[5] Smith L, Foxcroft D. Drinking in the UK, An exploration of Trends. Joseph Rowntree Foundation 2009.

[6] MacGregor GS, Hashem KM. Action on sugar—lessons from UK salt reduction programme. *Lancet* 2014;**383**:929–931.

[7] Website available at: http://www.parliament.uk/business/publications/research/briefing-papers/SN05021/alcohol-minimum-pricing [Last accessed 7th May 2015].

[8] Website available at: http://www.bsg.org.uk/clinical/commissioning-report/management-of-patients-with-chronic-liver-diseases.html [Last accessed 6th February 2016].

[9] Ratib S, Fleming KM, Crooks CJ *et al*. 1 and 5 year survival estimates for people with cirrhosis of the liver in England, 1998–2009: A large population study. *Journal of Hepatology* 2014**;60:**282–289.

[10] Ratib S, Fleming KM, Crooks CJ *et al*. Causes of Death in People with Liver Cirrhosis in England Compared with the General Population: A Population-Based Cohort Study. *Am J Gastroenterol***.** 2015.

[11] Roberts SE, Goldacre MJ, Yeates D. Trends in mortality after hospital admission for liver cirrhosis in an English population from 1968 to 1999. *Gut*. 2005;**54**:1615–21.

[12] Jepsen P, Vilstrup H, Andersen PK *et al*. Comorbidity and survival of Danish cirrhosis patients: a nationwide population-based cohort study. *Hepatology.* 2008**; *48*** (1):214-20.

[13] SriRajaskanthan R, Preedy V. Diagnosis and management of alcoholic liver disease, a review. *Clinical Effectiveness in Nursing*. 2006; **9**, Supplement 3(0):e286–e94.

[14] Leon DA, McCambridge J. Liver cirrhosis mortality rates in Britain from 1950 to 2002: an analysis of routine data. *Lancet*. 2006; **367**(9504):52–6.

[15] WHO. http://www.who.int/classifications/icd/en/ [Last accessed 6th February 2016]**.**

[16] Liu B, Balkwill A, Reeves G *et al*. Body mass index and risk of liver cirrhosis in middle aged UK women: prospective study. *BMJ*. 2010;**340**:c912.

[17] Jepsen P, Vilstrup H, Sorensen HT. Alcoholic cirrhosis in Denmark - population-based incidence, prevalence, and hospitalization rates between 1988 and 2005: a descriptive cohort study. *BMC Gastroenterol*. 2008;**8**(3).

[18] ICD version 8: http://www.wolfbane.com/icd/icd8.htm [Last accessed 6th February 2016]

[19] ICD version 9: http://en.wikipedia.org/wiki/List_of_ICD-9_codes [Last accessed 6th February 2016]

[20] Hanley A, Hubbard RB, Navaratnam V. Mortality trends in Asbestosis, Extrinsic Allergic Alveolitis and Sarcoidosis in England and Wales. *Respiratory Medicine*. 2011;**105**(9):1373–1379.

[21] Liver disease in Wales: https://assemblyinbrief.wordpress.com/2015/05/11/liver-disease-in-wales [Last accessed 6th February 2016]

[22] Blachier M, Leleu, H, Peck-Radosavljevic M *et al*. The burden of liver disease in Europe: A review of available epidemiological data. *Journal of Hepatology. 2013;***58:**593–608.

[23] Campbell J, Dedman DJ, Eaton SC *et al*. Is the CPRD GOLD population comparable to the U.K. population? *Pharmacoepidemiol Drug Saf* 2013;**22**(suppl1):280.

[24] Navaratnam V, Fleming KM, West J *et al*. The rising incidence of idiopathic pulmonary fibrosis in the UK. *Thorax. 2011;* **66**(6):462–467.

[25] Halliday ML, Coates RA, Rankin JG. Changing Trends of Cirrhosis Mortality in Ontario, Canada, 1911–1986. *International Journal of Epidemiology*.1991;**20**(1):199–208.

[26] Bosetti C, Levi F, Luchinni F *et al*. Worldwide mortality from cirrhosis: An update to 2002. *Journal of Hepatology*.2007*;***46:**827–839.

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Guarantor of the article: S.R accepts full responsibility for the conduct of the study and had access to the data and control of the decision to publish. The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted.

Specific author contribution: K.M.F. had the original idea for the study and all authors contributed to its interpretation. S.R was responsible for data management, the statistical analysis and wrote the first draft of the paper. K.M.F. and J.W. revised the paper critically and all authors approved the final version. The funders of this study had no role in the design, analysis or interpretation of the data.).

Ethics: Approval was given by the Independent Scientific and Ethical Committee of the CPRD for the CPRD study (09_065RA_3). Ethical approval was not required for the use of Office for National Statistics mortality data.

Data sharing: Patient level data and full dataset and technical appendix and statistical code are available from the corresponding author S.R. Consent was not obtained but the presented data are anonymised and risk of identification is low.

Figure 1 Standardised mortality rates for England and Wales, 1968-2011, for liver disease and different definitions† of cirrhosis. Standardised incidence rates for definition 3, from 1998 to 2009.

Figure 2 Standardised mortality and incidence rates by age-group in men, according to cirrhosis definitions 1 and 3.

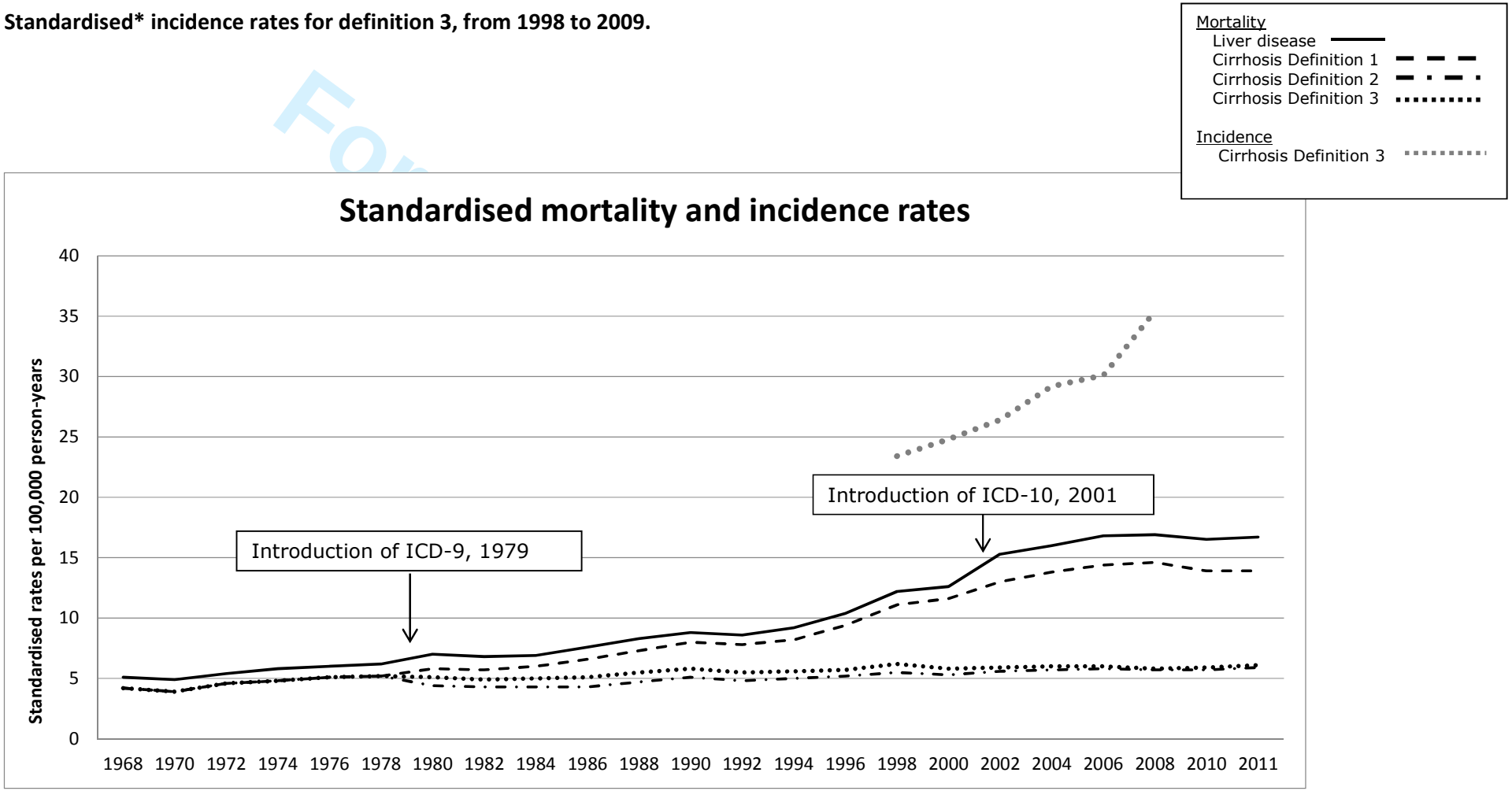
Figure 3 Standardised mortality and incidence rates by age-group in women, according to liver cirrhosis definitions 1 and 3.

ICD description	ICD-9 code	ICD-10 code	Liver cirrhosis-definition 1		Liver cirrhosis-definition 3	
			1992	2008	1992	2008
			n=3050	n=6469	n=2118	n=2584
Alcoholic fatty liver	5710	K70.0	34 (1·1)	229 (3·5)	-	-
Acute alcoholic hepatitis	5711	K70.1	77 (2·5)	148 (2·3)	-	-
Alcoholic cirrhosis of liver	5712	K70.3	749 (24·6)	1018 (15·7)	749 (35·4)	1018 (39·4)
Alcoholic liver damage, unspecified	5713	K70.9	647 (21·2)	2594 (40·1)	-	-
Chronic hepatitis	5714	K73.9	95 (3·1)	6 (0·1)	-	-
Cirrhosis of liver without mention of alcohol/other and unspecified cirrhosis of liver	5715	K74.6	1106 (36·3)	1485 (23)	1106 (52·2)	1485 (57·5)
Biliary cirrhosis	5716	K74.5	206 (6·8)	9 (0·1)	206 (9·7)	9 (0·3)
Other chronic non-alcoholic liver disease	5718		52 (1·7)	-		
Unspecified chronic liver disease without mention of alcohol	5719		84 (2·8)	-		
Oesophageal varices with bleeding	4560	I85.0	-	-	42 (2·0)	35 (1·4)
Oesophageal varices without bleeding	4561	I85.9	-	-	15 (0·7)	6 (0·2)
Alcoholic fibrosis and sclerosis of liver		K70.2	-	1 (0·02)	-	-
Alcoholic hepatic failure		K70.4	-	774 (12)	-	-
Chronic hepatic failure		K72.1	-	-	-	10 (0·4)
Chronic active hepatitis, not elsewhere classified		K73.2	-	58 (0·9)	-	-
Hepatic fibrosis		K74.0	-	5 (0·08)	-	-
Hepatic sclerosis		K74.1	-	1 (0·02)	-	-
Primary biliary cirrhosis		K74.3	-	137 (2·1)	-	-
Secondary biliary cirrhosis		K74.4	-	<5 (0·1)	-	<5 (0·2)
Other and unspecified cirrhosis of liver		K74.6	-	-	-	-
Portal hypertension		K76.6	-	-	-	17 (0·7)

Table 1 Distribution of causes of death for liver cirrhosis definitions 1 and 3 in 1992 and 2008, n (%)

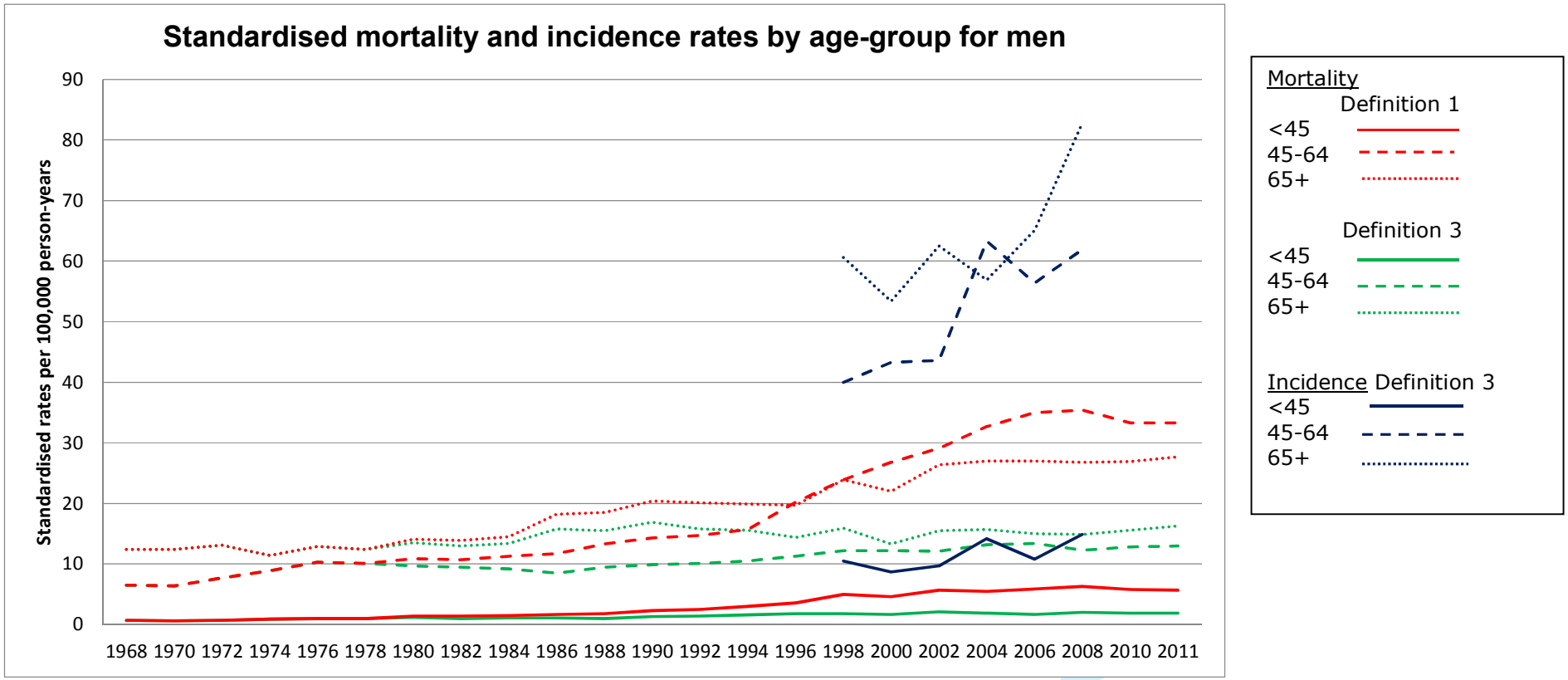
Figure 1 Standardised* mortality rates for England and Wales, 1968-2011, for liver disease and different definitions† of cirrhosis.

Standardised* incidence rates for definition 3, from 1998 to 2009.



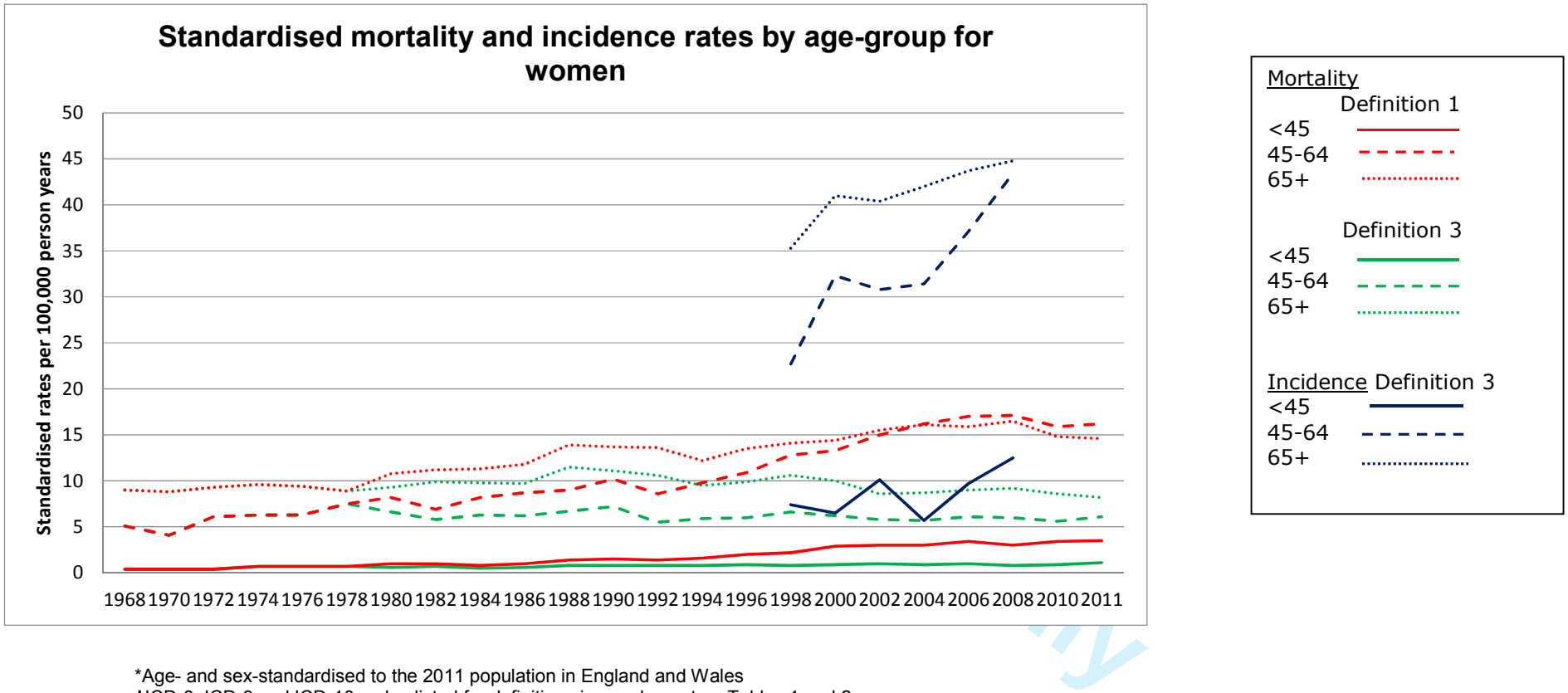
*Age- and sex-standardised to the 2011 population in England and Wales. †ICD-8, ICD-9 and ICD-10 codes listed for each definition in supplementary Tables 1 and 2. . ¥ Liver disease defined as ICD10 codes for 'Diseases of the Liver' K70-K77 (or equivalent ICD8 and ICD9codes-see supplementary Tables 1 and 2).

Figure 2 Standardised* mortality and incidence¥ rates by age-group in men, according to cirrhosis definitions 1 and 3†



*Age- and sex-standardised to the 2011 population in England and Wales
†ICD-8, ICD-9 and ICD-10 codes listed for definitions in supplementary Tables 1 and 2
¥ Incidence estimates taken from Ratib et al.[3]

Figure 3 Standardised* mortality and incidence¥ rates by age-group in women, according to cirrhosis definitions 1 and 3†



*Age- and sex-standardised to the 2011 population in England and Wales
†ICD-8, ICD-9 and ICD-10 codes listed for definitions in supplementary Tables 1 and 2
¥ Incidence estimates taken from Ratib et al.[3]

Supplementary Table 1 ICD -8 and ICD- 9 codes for liver disease and the three definitions of liver cirrhosis (LC)

ICD version	Code	Description	Liver disease	LC Definition 1†	LC Definition 2§	LC Definition 3¥
ICD-8	5700	Acute/subacute necrosis of liver	Yes	No	No	No
	5710	Cirrhosis of liver-alc	Yes	Yes	Yes	Yes
	5719	Cirrhosis of liver-othe	Yes	Yes	Yes	Yes
	5720	Supperative hepatitis and liver abscess	Yes	No	No	No
	5730	Other disease of liver	Yes	No	No	No
ICD-9	570	Acute/subacute necrosis of liver	Yes	No	No	No
	5710	Alcoholic fatty liver	Yes	Yes	No	No
	5711	Acute alcoholic hepatitis	Yes	Yes	No	No
	5712	Alcoholic cirrhosis of liver	Yes	Yes	Yes	Yes
	5713	Alcoholic liver damage, unspec	Yes	Yes	No	No
	5714	Chronic hepatitis	Yes	Yes	No	No
	5715	Cirrhosis of liver without mention of alcohol	Yes	Yes	Yes	Yes
	5716	Biliary cirrhosis	Yes	Yes	No	Yes
	5718	Other chronic nonalcoholic liver disease	Yes	Yes	No	No
	5719	Unspec chronic liver disease without mention of alcohol	Yes	Yes	No	No
	5720	Abscess of liver	Yes	No	No	No
	5721	Portal pyemia	Yes	No	No	No
	5722	Hepatic coma	Yes	No	No	No
	5723	Portal hypertension	Yes	No	No	Yes
	5724	Hepatorenal syndrome	Yes	No	No	No
	5728	Other sequelae of chronic liver disease	Yes	No	No	No
	573	Other disorders of liver	Yes	No	No	No
	4560	Oesophageal varices with bleeding	No	No	No	Yes

4561	Oesophageal varices without bleeding	No	No	No	Yes
4562	Oesophageal varices in diseases classified elsewhere	No	No	No	Yes

†Leon et al.[13] §Jepsen et al.[16]¥ Ratib et al.[3]

Supplementary Table 2 ICD -10 codes for liver disease and the three definitions of liver cirrhosis (LC)

ICD version	Code	Description	Liver disease	LC Definition 1†	LC Definition 2§	LC Definition 3¥
ICD-10	K70.0	Alcoholic fatty liver	Yes	Yes	No	No
	K70.1	Alcoholic hepatitis	Yes	Yes	No	No
	K70.2	Alcoholic fibrosis and sclerosis of liver	Yes	Yes	No	No
	K70.3	Alcoholic cirrhosis of liver	Yes	Yes	Yes	Yes
	K70.4	Alcoholic hepatic failure	Yes	Yes	No	No
	K70.9	Alcoholic liver disease, unspecified	Yes	Yes	No	No
	K71.0	Toxic liver disease with cholestasis	Yes	No	No	No
	K71.1	Toxic liver disease with hepatic necrosis	Yes	No	No	No
	K71.2	Toxic liver disease with acute hepatitis	Yes	No	No	No
	K71.3	Toxic liver disease with chronic persistent hepatitis	Yes	No	No	No
	K71.4	Toxic liver disease with chronic lobular hepatitis	Yes	No	No	No
	K71.5	Toxic liver disease with chronic active hepatitis	Yes	No	No	No
	K71.6	Toxic liver disease with hepatitis, not elsewhere classified	Yes	No	No	No
	K71.7	Toxic liver disease with fibrosis and cirrhosis of liver	Yes	No	No	Yes
	K71.8	Toxic liver disease with disorders of liver	Yes	No	No	No
	K71.9	Toxic liver disease with disorders of liver	Yes	No	No	No
	K72.0	Acute and subacute hepatic failure	Yes	No	No	No
	K72.1	Chronic hepatic failure	Yes	No	No	Yes
	K72.9	Hepatic failure, unspecified	Yes	No	No	No
	K73	Chronic hepatitis, not elsewhere classified	Yes	Yes	No	No

†Leon et al.[13] §Jepsen et al.[16] ¥ Ratib et al.[3] LC=liver cirrhosis

ICD version	Code	Description	Liver disease	LC Defintion2†	LC Defintion2§	LC Defintion3¥
ICD-10	K74.0	Hepatic fibrosis	Yes	Yes	No	No
	K74.1	Hepatic sclerosis	Yes	Yes	No	No
	K74.2	Hepatic fibrosis with hepatic sclerosis	Yes	Yes	No	No
	K74.3	Primary Biliary cirrhosis	Yes	Yes	No	No
	K74.4	Secondary biliary cirrhosis	Yes	Yes	No	Yes
	K74.5	Biliary cirrhosis, unspecified	Yes	Yes	No	Yes
	K74.6	Other and unspecified cirrhosis of liver	Yes	Yes	Yes	Yes
	K75	Other inflammatory liver diseases	Yes	No	No	No
	K76.0	Other diseases of liver	Yes	No	No	No
	K76.1	Chronic passive congestion of liver	Yes	No	No	No
	K67.2	Central haemorrhagic necosis of liver	Yes	No	No	No
	K76.3	Infarction of liver	Yes	No	No	No
	K76.4	Peliosis hepatis	Yes	No	No	No
	K76.5	Hepatic veno-occlusive disease	Yes	No	No	No
	K76.6	Portal hypertension	Yes	No	No	Yes
	K76.7	Hepatorenal syndrome	Yes	No	No	No
	K76.8	Other specified diseases of liver	Yes	No	No	No
	K76.9	Liver disease, unspecified	Yes	No	No	No
	K77	Liver disorders in diseases classified elsewhere	Yes	No	No	No
	I85.0	Oesophageal varices with bleeding	No	No	No	Yes
	I85.9	Oesophageal varices without bleeding	No	No	No	Yes
	I86.4	Gastric varices	No	No	No	Yes
	I98.2	Oesophageal varices in diseases classified elsewhere	No	No	No	Yes

†Leon et al.[13] §Jepsen et al.[16] ¥ Ratib et al.[3] LC=liver cirrhosis

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
(Title and abstract	1	*(a)* Indicate the study's design with a commonly used term in the title or the abstract p.1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found p.2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported p.4
Objectives	3	State specific objectives, including any prespecified hypotheses p.5
Methods		
Study design	4	Present key elements of study design early in the paper p.6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection p.6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up p.6 *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable p.6/7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group p.6
Bias	9	Describe any efforts to address potential sources of bias p.7
Study size	10	Explain how the study size was arrived at N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why p.7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding p.7
		(*b*) Describe any methods used to examine subgroups and interactions p.7
		(*c*) Explain how missing data were addressed N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed N/A *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses N/A

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed N/A
		(b) Give reasons for non-participation at each stage N/A
		(c) Consider use of a flow diagram N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders N/A
		(b) Indicate number of participants with missing data for each variable of interest N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time p.8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included p.8
		(*b*) Report category boundaries when continuous variables were categorized p.7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses p.10
Discussion		
Key results	18	Summarise key results with reference to study objectives p.11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias p.11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence p.12
Generalisability	21	Discuss the generalisability (external validity) of the study results p.11/13
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based p.18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Liver cirrhosis in England-an observational study. Are we measuring its burden correctly?

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Liver cirrhosis in England-an observational study. Are we measuring its burden occurrence correctly?

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Abbreviations: ONS-Office for National Statistics; ICD10-International Classification of Disease 10th version

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Abstract

Objectives: Mortality due to liver disease (of which cirrhosis is the end-stage) is increasing more than any other chronic condition in the UK. This study aims to demonstrate that (i) exclusive reliance on mortality rates may not reveal the true burden of liver cirrhosis, and (ii) diverse use of diagnostic coding may produce misleading estimates.

Design: Observational study

Setting: The Office for National Statistics death registry was interrogated to investigate liver cirrhosis mortality trends in England and Wales, from 1968 to 2011.

Main outcome: Standardised mortality trends according to three different definitions of liver cirrhosis based on the specificity of diagnostic codes were calculated: 1(chronic liver diseases), 2 (alcoholic and unspecified cirrhosis only) and 3 (cirrhosis as end-stage liver disease). The mortality trends were compared to incidence rates established in a previous population-based study (based on definition 3), from 1998 to 2009, to investigate discrepancies between these two measures.

Results: Over the study period, the overall standardised liver cirrhosis mortality rates were 8·8, 5·1 and 5·4 per 100,000 person-years for definitions 1, 2 and 3 of respectively. The mortality rates for definition 3 in 1998 and 2009 were 6·2 and 5·9 per 100,000 person-years respectively; whilst the equivalent incidence rates were at least three- and six-fold higher: 23·4 and 35·9 per 100,000 person-years respectively. This discrepancy between incidence and mortality rates was also at least three-fold in men and women separately, and across age-groups.

Conclusion: Mortality rates underestimated the incidence of liver cirrhosis by at least three-fold between 1998 and 2009 and varied with differing definitions of disease. Mortality data should not be used exclusively as an indicator for the occurrence of liver cirrhosis in the population. Routinely collected healthcare data are available to measure occurrence of this disease. Careful consideration should be taken when selecting diagnostic codes for cirrhosis.

Key words: Liver cirrhosis, Mortality, Incidence, Routine data

Article summary

Strengths and limitations of this study

- First study to quantify the difference in liver cirrhosis mortality rates based on different definitions of disease.
- First study to demonstrate that overall mortality rates underestimate the incidence of liver cirrhosis by at least three-fold.
- A key strength of the study is the large number of registered deaths and the long period of time that the data were obtained over.
- A potential limitation of death registry data is the change in coding practice over time.
- The Office for National Statistics data cover deaths in England and Wales combined whereas the incidence data are based solely on English general practices.

INTRODUCTION

Liver disease, of which liver cirrhosis is the end-stage, constitutes the third commonest cause of premature death in the UK.[1] According to the UK's current Chief Medical Officer (CMO), the rate of increase in premature mortality from liver disease and from cirrhosis is substantially higher in the UK than other countries in Western Europe.[2] Further, cirrhosis per se has recently been reported to be increasing in the UK at a faster rate than the top four most-commonly diagnosed cancers (lung, breast, bowel and prostate).[3] The main reasons for the rise in cirrhosis are probably parallel increases in alcohol consumption and obesity.[1,4] In the UK, alcohol consumption per person across the population has more than doubled in the last half-century and one in four adults are now considered to be obese.[5,6] These are preventable causes and interventions such as minimum pricing for alcoholic drinks and campaigns for healthier lifestyles have been considered as part of a strategy to reduce liver disease.[7,8]

Despite its 5-year mortality being equivalent to that seen in colon cancer, and in contrast to the monitoring of new cancer diagnoses, there is no mandatory registration of cirrhosis cases in the UK or elsewhere in the world.[9] Estimates of the occurrence of cirrhosis, and consequently the assessment of success or failure of primary interventions, have therefore been primarily drawn from death registry data.[1,2] This methodology is likely to mask the true incidence of cirrhosis. Firstly, not everyone with cirrhosis dies directly due to the disease and our recent population-based study estimated that only 32% of deaths in people with cirrhosis had a cirrhosis related code anywhere on their death certificate.[10] Secondly, there is a time-lag between diagnosis and death. Hospital-based studies have reported survival estimates at 1-year of around 65%.[11,12] Those who do not die immediately after diagnosis, and those who do not die directly from the disease, will not be accounted for by reliance on the death registry.

Establishing accurate estimates of cirrhosis is further compounded by the fact that there is no clear boundary between liver disease and cirrhosis. There are a myriad of liver diseases and for each one patients progress to cirrhosis at different rates, if at all.[13] Previous authors of well cited papers have used a range of codes representing different liver diseases when reporting mortality due to "liver cirrhosis".[11,12,14] Subsequently it is often not possible to determine whether authors are truly examining liver disease or cirrhosis per se.

In the UK, as in many Northern European countries, patients with suspected liver cirrhosis may be diagnosed by their primary care physician, or more commonly are referred to a secondary care specialist who will then pass on information to the primary care physician. Our research group has therefore used linked primary and secondary routine healthcare databases in order to capture the incidence of cirrhosis as comprehensively as possible. [3] Given the dependence of health service planning on accurate knowledge of occurrence of disease, we sought to use routinely available data to (i) examine how cirrhosis mortality rates may differ according to the range of specificity of diagnostic codes used within the hepatology community; and (ii) quantify the difference between cirrhosis mortality rates (from death registry data) and cirrhosis incidence rates (previously established) from linked routine healthcare databases) based on the same definition of disease and over the same time period

METHODS

Data sources

We obtained mortality data from the Office for National Statistics (ONS) website (www.ons.gov.uk). These data are derived from registered death certificates and consist of counts of death by underlying cause (based on the International Classification of Disease (ICD)[15]) year of death, 5-year age-group, and sex for England and Wales from 1968 to 2011. Population data for the respective years were also obtained from the ONS website stratified by 5-year age-group and sex. We used the linked Clinical Practice Research Datalink (CPRD) and English Hospital Episodes Statistics (HES) to conduct a cohort study identify incident diagnoses of cirrhosis between 1998 and 2009 (n=5118). The diagnoses in the CPRD are made by histological examination and/or characteristic clinical signs of advanced liver disease.[3]

Definitions of cirrhosis

We used three definitions of cirrhosis according to the specificity of ICD diagnostic coding:

Definition 1: This code list was developed by Leon et al.[14] for international comparisons and has been selected as it is a relatively broad definition of cirrhosis and includes other chronic liver disease (e.g. alcoholic liver disease and chronic hepatitis), and has been used widely by other authors.[16]

Definition 2: This is a restrictive definition used by Jepsen et al.[17], including only alcoholic and unspecified cirrhosis of the liver.

Definition 3: This code list reflects cirrhosis as the end-stage of liver disease and includes codes for portal hypertension and oesophageal varices which are not included in the above definitions. This code list is the same definition our group has used previously to define a cohort of people with an incident diagnosis of cirrhosis in England using the linked CPRD and HES.[3]

To provide a context, we combined all liver diseases according to ICD version 10 chapter 'Diseases of the Liver' (K70-K77) and refer to this this category as 'Liver disease'. During the calendar period considered three different revisions of the ICD were used and mapping across these 3 versions are shown in Supplementary Tables 1 and 2.[15,18,19]

Statistical analysis

Mortality rates

Age at death was categorized from the age of 15 years in three groups (<45, 45-64 and ≥65 years). We determined crude mortality rates per 100,000 person-years from 1968 to 2011, for liver disease and all three definitions of cirrhosis. We calculated age- and sex-stratum specific cirrhosis mortality rates and applied these to the 2011 population to generate annual standardised mortality rates. Negative binomial regression modelling was used to estimate mortality rate ratios with adjustment for age and sex. We determined average annual increase.

Incidence rates

Determining the incidence of cirrhosis (using definition 3) has been described elsewhere.[3] In brief, we defined a cohort of incident diagnoses from the linked CPRD and English HES data from 1998 to 2009 for adults from the age of 18 years onwards. Estimates of incidence from the study have been standardised to the 2011 population and used in this current paper to make a direct comparison with standardised mortality rates over the same time period and using the same definition of disease.

RESULTS

Standardised mortality rates

The overall standardised mortality rates for definitions 1 to 3 of cirrhosis over the study period were 8.8 (95% CI 8·8, 8·8), 5.4 (95% CI 5·4, 5·5) and 5.1 (95% CI 5·0, 5·1) per 100,000 person-years, respectively. Figure 1 displays the standardised mortality trends from 1968 to 2011 for all definitions. There was only a marginal difference in absolute and relative terms between liver diseases combined and definition 1, and similarly only a marginal difference between definitions 2 and 3.

Between 1979 (the introduction of ICD-9) and 2001 (the introduction of ICD-10), the average annual relative increase in mortality from cirrhosis was 1.04 (95% CI 1.03, 1.04), 1.01 (95%CI 1.01, 1.01) and 1.01(95% CI 1.01, 1.02) for definitions 1, 2 and 3 respectively. From 2001 onwards the increase was smaller for all definitions: 1.00 (95%CI 1.00, 1.01), 1.00 (95%CI 0.99, 1.00) and 0.99(95%CI 0.99, 1.00) respectively.

From 1992 to 2008, the absolute difference in rates between those of definition 1 and definition 2 diverged further with time. For example, the absolute rates for definition 1 in 1992, 1996 and 2008 were 7·8, 9·4 and 14·6 per 100,000 person-years; the equivalent for definitions 2 and 3 were 4.8, 5.5 and 5.8, and 5·5, 5·7 and 5·8 respectively.

Change in cause of death over time

In order to explore possible reasons for the divergence in deaths between the different definitions of disease, from 1992 and 2008, we have presented the distribution of causes of death in 1992 and 2008 per definition (Supplementary Table 1). We have not displayed the distribution for definition 2 as it is similar to that of definition 3.

In 1992, the percentage of deaths attributed to alcoholic liver damage (ICD-9 5713), which is included in definition 1 but not in definition 3, was 21·2%. This increased to 40.1% in 2008 (ICD-10 K70.9). During the same time frame, the percentage of deaths due to alcoholic cirrhosis (ICD-9 5712) decreased from 24·6% to 15·7%. In contrast, the distribution of causes of death of definition 3 did not change that dramatically. For example, 35·4% of deaths in 1992 were due to alcoholic cirrhosis of the liver (ICD-9 5712) and the equivalent proportion in 2008 was 39·4% (ICD-10 K70.3). Similarly, the proportion of deaths due to cirrhosis without mention of alcohol was 52·2% in 1992 (ICD-9 5715) and 57·5% in 2008 (ICD-10 K74.6).

Comparison between mortality and incidence rates

In a previous study we determined the incidence of cirrhosis in England during the period 1998 to 2009 using definition 3 of cirrhosis.[3] These rates have been standardised to the 2011 population and inserted into Figure 1. Specifically, the standardised incidence rates were 23·4 and 35·9 per 100,000 person-years in 1998 and 2009 respectively. This is in sharp contrast to the standardised mortality rates of 6·2 and 5·9 per 100,000 person-years in 1998 and 2009 respectively (in England and Wales). The overall rate of change between 1998 and 2009 was 50.6% for incidence, whereas mortality rates decreased by 2·5% over the same time period. The mortality rates according to definition 1 were also substantially less than the estimates of incidence; 11·1 and 13·8 per 100,000 person-years in 1998 and 2009 respectively, equating to a rate of change of only 28·9% across the period (Figure 1).

For both sexes, the standardised incidence rates were between 3- and 6-fold that of mortality (definition 3), in all age-groups, across the study period (Figures 2 and 3). The incidence rates were also substantially higher than mortality rates based on definition 1, for both men and women and across all age-groups.

DISCUSSION

Main findings

We found that both the absolute and relative cirrhosis mortality rates varied with differing disease definition. The overall age-standardised mortality rates during 1968 to 2011 were 8·8, 5·1 and 5·4 per 100,000 person-years for definitions 1 to 3 respectively. Careful consideration should be taken when selecting diagnostic codes for cirrhosis so that they are in line with the research question and research wastage is minimised. Further, using different routinely available clinical datasets we have previously demonstrated that between 1998 and 2009 the incidence of cirrhosis increased by 50·6% which is in contrast to a decrease in mortality from cirrhosis of 2·5% based on the same definition of disease.[3] Cirrhosis incidence rates were consistently higher than mortality rates, at least three-fold between 1998 and 2009, independent of age and sex. Mortality rates should therefore not be used alone to monitor the occurrence of cirrhosis; alternative sources of routinely collected data should be considered.

Strengths and limitations

This is the first study to quantify the difference in cirrhosis mortality rates by differing definitions of disease and the first to compare cirrhosis mortality and incidence rates using the same definition of disease. Key strengths of the study are its external validity, the large number of registered deaths, and the long period of time that the data were obtained over. The latter meant that we were able to report trends of mortality rates for a period of more than forty years. A potential limitation of death registry data is the change in coding practice over time, known as coding phenomenon. The change in rate of specific causes of death over time could be due to the use of different ICD versions throughout the study period rather than a true change. For example, the sharp increase in the number of liver disease deaths (definition) 1, after 1979, when ICD-9 came into use; followed by a

reduction in the rate of change from 2001 onwards when ICD-10 came into place. This phenomenon has been reported by others.[20] Coding phenomenon also occurs when doctors change the way they select codes on death certificates. For example, over time doctors may be more likely to use codes for alcoholic liver disease even in the presence of alcoholic cirrhosis. This may explain the increase in deaths coded as alcoholic liver damage in contrast to the fall in deaths coded for alcoholic cirrhosis, which we report in this study. Despite the potential changes in coding practice over time, mortality rates using the broadest definition of liver disease are still dramatically lower than the incidence rates of cirrhosis reported using a relatively restricted definition. Finally, the ONS data cover deaths in England and Wales combined whereas the incidence data are based solely on English general practices so we are not exactly comparing like with like. However, given similar liver disease mortality in England and Wales,[21] if death registry data for England only were available and had been used the discrepancy between mortality and incidence would highly unlikely be less than that which we report and our conclusions would remain the same.

Implications

Our findings provide evidence that using mortality data alone to measure the occurrence of cirrhosis could have major implications on healthcare planning. Given the sharp rise in cirrhosis incidence in the last decade that is not visible from mortality statistics, the NHS may well be under resourced and unable to cope with future demand on hepatology clinics. Mortality and incidence are two very different measures of disease burden. If only cirrhosis which leads to death from cirrhosis is of importance to clinicians and policy makers then measuring mortality is indeed the more appropriate measure. However if we are truly concerned with measuring the occurrence of cirrhosis and/or the impact of public health intervention strategies then incidence rates are crucial. When establishing the success of public health interventions aimed at reducing new disease, such as alcohol policies and healthy eating campaigns it is essential to set targets for incidence to determine if these sorts of

interventions have been effective or not. Evaluation of such interventions needs to account for the long sojourn between disease onset and fibrosis/cirrhosis, which can take between 10 and 30 years.[22] Mortality is even further away therefore even less relevant a measure than incidence. The study by Leon et al.[14] (definition 1) used mortality rates as they were believed to be important indicators of population levels of alcohol harm. However, our findings suggest that the use of incidence rates would have been more indicative. Finally, differences in incidence and mortality could be partially due to improvement in treatment and care of chronic liver disease, if anything this means that with improving treatment mortality becomes an even worse proxy measure of burden. One recommendation for future work, from this study, is to measure the incidence of cirrhosis by using routinely collected healthcare data often known as 'Big Data'. Such data are becoming increasingly familiar and accepted in hepatology with, for example, the recent Lancet Commission recommending non-alcoholic fatty liver disease prevalence be measured by establishing a cohort from primary care data.[1] The strengths of using routinely collected data are from methodological and cost-effectiveness perspectives. Firstly, the recent linkage of primary care and secondary care allows a representative cohort of patients covering the full spectrum of disease to be identified, representative of the English population.[3,23] Secondly, accessing large amounts of routinely collected data for chronic diseases is substantially cheaper than establishing a bespoke prospective cohort of patients and following them potentially for several decades. Similar discrepancies between mortality and incidence figures have been shown in other diseases for which there is no mandatory recording such as idiopathic pulmonary fibrosis.[24] Routinely collected data may be appropriate to measure the incidence of this condition too.

The second implication of our findings is the necessity of careful consideration of disease definition. We have shown that the inclusion of patients who died from chronic liver diseases introduced an overestimate of cirrhosis mortality rates, by about 60%, comparing definitions 1 and 3 (8·8 per 100,000 vs. 5·4, respectively). Definition 1 included codes related to alcoholic liver disease such as

alcoholic fatty liver disease (K70.0) and alcohol liver disease (K70.9) (the latter contributed 40% of 'Definition 1' deaths in 2008) , as well as autoimmune diseases, which were not included in Definition 3. With respect to alcoholic liver disease, some patients with this condition can fluctuate between alcoholic fatty liver and alcoholic hepatitis and not actually completely progress to cirrhosis, and if they stop drinking the architecture of their liver may return to normal.[13] Consequently, on one hand, it may be misleading to include codes such as alcoholic fatty liver disease (K70.0), alcoholic hepatitis (K70.1) and alcohol liver disease (K70.9) when intending to measure deaths due to cirrhosis. Conversely, one could argue that as these diagnostic codes represent diseases which could be a pre-cursor to cirrhosis they could actually reflect a poor specification of decompensated disease and hence cirrhosis. For example, this current study has shown that a particular difference between definitions 1 and 3 in the rate of change cirrhosis between 1992 and 2008 may have been mediated through an increase in deaths coded as the broader term "alcoholic liver disease" with a concomitant decline in the number of deaths coded as the more specific "alcoholic cirrhosis". One cannot disprove the possibility of an artefactual difference due to clinicians' certification practice rather than a true increase in alcoholic liver disease compared to alcoholic cirrhosis. Therefore, it may indeed be appropriate to use broader codes like alcoholic liver disease in order to capture patients with cirrhosis who may not have been certified as dying from cirrhosis per se. The key point is that code lists should reflect the precise research question that is being posed, otherwise results are misleading. Future research should take this finding into account. We acknowledge that specific ICD10 codes for chronic viral hepatitis such as chronic hepatitis B (B18.1) and chronic hepatitis C (B18.2) have not been considered by researchers in the field. Inclusion of these codes could also be considered when developing a broad definition of cirrhosis.

Conclusion

This study has highlighted that reliance on mortality data alone may lead to an underestimate of the occurrence of cirrhosis, and indeed liver disease in general. Consequently the occurrence of liver disease in England is likely to be considerably greater than that which others report, including the current UK CMO.[1,2,25,26] Alternative sources of routinely collected data should be considered as a matter of urgency and appropriate definitions of disease employed. Accurate monitoring of the incidence of cirrhosis will allow the optimisation of limited healthcare services and provide appropriate baseline figures from which to evaluate intervention, particularly those implemented at population level.

References

[1] Williams R, Aspinall R, Bellis M *et al*. 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. *Lancet* 2014;**384**:1953–1997.

[2] CMO report 2012 [Internet]. Available at https://www.gov.uk/government/publications/cmo-annual-report-2011-volume-one [last accessed 6th February 2016].

[3] Ratib S, West J, Crooks CJ *et al*. Diagnosis of Liver Cirrhosis in England, a Cohort Study, 1998-2009: A Comparison With Cancer. *Am J Gastroenterol* 2014;**109**:190–198.

[4] von Wulffen, M, Clark PJ, Macdonald GA *et al.* Liver-related mortality in countries of the developed world: an ecological study approach to explain the variability. Alimentary Pharmacology & Therapeutics 2016; **44**(1): 68-77.

[5] Smith L, Foxcroft D. Drinking in the UK, An exploration of Trends. Joseph Rowntree Foundation 2009.

[6] MacGregor GS, Hashem KM. Action on sugar—lessons from UK salt reduction programme. *Lancet* 2014;**383**:929–931.

[7] Website available at: http://www.parliament.uk/business/publications/research/briefing-papers/SN05021/alcohol-minimum-pricing [Last accessed 7th May 2015].

[8] Website available at: http://www.bsg.org.uk/clinical/commissioning-report/management-of-patients-with-chronic-liver-diseases.html [Last accessed 6th February 2016].

[9] Ratib S, Fleming KM, Crooks CJ *et al*. 1 and 5 year survival estimates for people with cirrhosis of the liver in England, 1998–2009: A large population study. *Journal of Hepatology* 2014**;60:**282–289.

[10] Ratib S, Fleming KM, Crooks CJ *et al*. Causes of Death in People with Liver Cirrhosis in England Compared with the General Population: A Population-Based Cohort Study. *Am J Gastroenterol***.** 2015.

[11] Roberts SE, Goldacre MJ, Yeates D. Trends in mortality after hospital admission for liver cirrhosis in an English population from 1968 to 1999. *Gut*. 2005;**54**:1615–21.

[12] Jepsen P, Vilstrup H, Andersen PK *et al*. Comorbidity and survival of Danish cirrhosis patients: a nationwide population-based cohort study. *Hepatology.* 2008**;** ***48*** (1):214-20.

[13] SriRajaskanthan R, Preedy V. Diagnosis and management of alcoholic liver disease, a review. *Clinical Effectiveness in Nursing*. 2006; **9**, Supplement 3(0):e286–e94.

[14] Leon DA, McCambridge J. Liver cirrhosis mortality rates in Britain from 1950 to 2002: an analysis of routine data. *Lancet*. 2006; **367**(9504):52–6.

[15] WHO. http://www.who.int/classifications/icd/en/ [Last accessed 6th February 2016]**.**

[16] Liu B, Balkwill A, Reeves G *et al*. Body mass index and risk of liver cirrhosis in middle aged UK women: prospective study. *BMJ*. 2010;**340**:c912.

[17] Jepsen P, Vilstrup H, Sorensen HT. Alcoholic cirrhosis in Denmark - population-based incidence, prevalence, and hospitalization rates between 1988 and 2005: a descriptive cohort study. *BMC Gastroenterol*. 2008;**8**(3).

[18] ICD version 8: http://www.wolfbane.com/icd/icd8.htm [Last accessed 6th February 2016]

[19] ICD version 9: http://en.wikipedia.org/wiki/List_of_ICD-9_codes [Last accessed 6th February 2016]

[20] Hanley A, Hubbard RB, Navaratnam V. Mortality trends in Asbestosis, Extrinsic Allergic Alveolitis and Sarcoidosis in England and Wales. *Respiratory Medicine*. 2011;**105**(9):1373–1379.

[21] Liver disease in Wales: https://assemblyinbrief.wordpress.com/2015/05/11/liver-disease-in-wales [Last accessed 6th February 2016]

[22] Blachier M, Leleu, H, Peck-Radosavljevic M *et al*. The burden of liver disease in Europe: A review of available epidemiological data. *Journal of Hepatology. 2013;***58:**593–608.

[23] Campbell J, Dedman DJ, Eaton SC *et al*. Is the CPRD GOLD population comparable to the U.K. population? *Pharmacoepidemiol Drug Saf* 2013;**22**(suppl1):280.

[24] Navaratnam V, Fleming KM, West J *et al*. The rising incidence of idiopathic pulmonary fibrosis in the UK. *Thorax. 2011;* **66**(6):462–467.

[25] Halliday ML, Coates RA, Rankin JG. Changing Trends of Cirrhosis Mortality in Ontario, Canada, 1911–1986. *International Journal of Epidemiology*.1991;**20**(1):199–208.

[26] Bosetti C, Levi F, Luchinni F *et al*. Worldwide mortality from cirrhosis: An update to 2002. *Journal of Hepatology*.2007*;***46:**827–839.

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Guarantor of the article: S.R accepts full responsibility for the conduct of the study and had access to the data and control of the decision to publish. The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted.

Specific author contribution: J.W. had the original idea for the study and all authors contributed to its interpretation. S.R was responsible for data management, the statistical analysis and wrote the

first draft of the paper. K.M.F. and J.W. revised the paper critically and all authors approved the final version. The funders of this study had no role in the design, analysis or interpretation of the data.

Ethics: Approval was given by the Independent Scientific and Ethical Committee of the CPRD for the CPRD study (09_065RA_3). Ethical approval was not required for the use of Office for National Statistics mortality data.

Data sharing: Patient level data and full dataset and technical appendix and statistical code are available from the corresponding author S.R. Consent was not obtained but the presented data are anonymised and risk of identification is low.

Figure 1 Standardised mortality rates for England and Wales, 1968-2011, for liver disease and different definitions† of cirrhosis. Standardised incidence rates for definition 3, from 1998 to 2009.

Figure 2 Standardised mortality and incidence rates by age-group in men, according to cirrhosis definitions 1 and 3.

Figure 3 Standardised mortality and incidence rates by age-group in women, according to liver cirrhosis definitions 1 and 3.

ICD description	ICD-9 code	ICD-10 code	Liver cirrhosis-definition 1		Liver cirrhosis-definition 3	
			1992	2008	1992	2008
			n=3050	n=6469	n=2118	n=2584
Alcoholic fatty liver	5710	K70.0	34 (1·1)	229 (3·5)	-	-
Acute alcoholic hepatitis	5711	K70.1	77 (2·5)	148 (2·3)	-	-
Alcoholic cirrhosis of liver	5712	K70.3	749 (24·6)	1018 (15·7)	749 (35·4)	1018 (39·4)
Alcoholic liver damage, unspecified	5713	K70.9	647 (21·2)	2594 (40·1)	-	-
Chronic hepatitis	5714	K73.9	95 (3·1)	6 (0·1)	-	-
Cirrhosis of liver without mention of alcohol/other and unspecified cirrhosis of liver	5715	K74.6	1106 (36·3)	1485 (23)	1106 (52·2)	1485 (57·5)
Biliary cirrhosis	5716	K74.5	206 (6·8)	9 (0·1)	206 (9·7)	9 (0·3)
Other chronic non-alcoholic liver disease	5718		52 (1·7)	-		
Unspecified chronic liver disease without mention of alcohol	5719		84 (2·8)	-		
Oesophageal varices with bleeding	4560	I85.0	-	-	42 (2·0)	35 (1·4)
Oesophageal varices without bleeding	4561	I85.9	-	-	15 (0·7)	6 (0·2)
Alcoholic fibrosis and sclerosis of liver		K70.2	-	1 (0·02)	-	-
Alcoholic hepatic failure		K70.4	-	774 (12)	-	-
Chronic hepatic failure		K72.1	-	-	-	10 (0·4)
Chronic active hepatitis, not elsewhere classified		K73.2	-	58 (0·9)	-	-
Hepatic fibrosis		K74.0	-	5 (0·08)	-	-
Hepatic sclerosis		K74.1	-	1 (0·02)	-	-
Primary biliary cirrhosis		K74.3	-	137 (2·1)	-	-
Secondary biliary cirrhosis		K74.4	-	<5 (0·1)	-	<5 (0·2)
Other and unspecified cirrhosis of liver		K74.6	-	-	-	-
Portal hypertension		K76.6	-	-	-	17 (0·7)

Table 1 Distribution of causes of death for liver cirrhosis definitions 1 and 3 in 1992 and 2008, n (%)

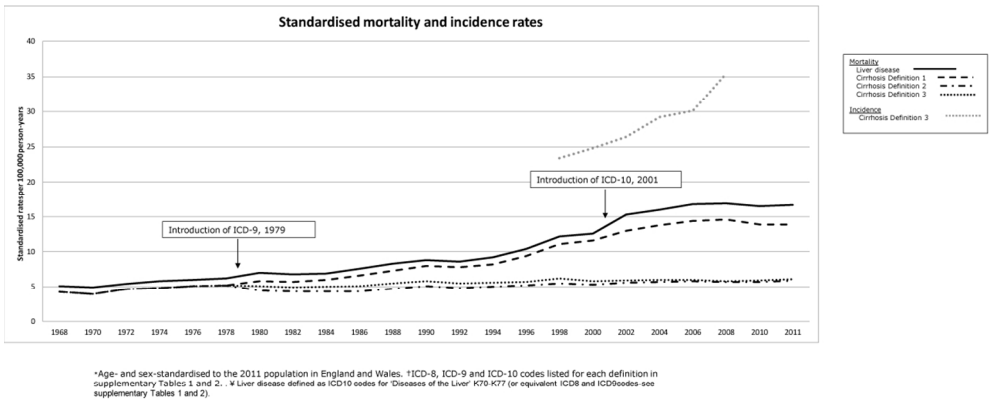


Figure 1 Standardised* mortality rates for England and Wales, 1968-2011, for liver disease and different definitions† of cirrhosis. Standardised* incidence rates for definition 3, from 1998 to 2009.

109x51mm (300 x 300 DPI)

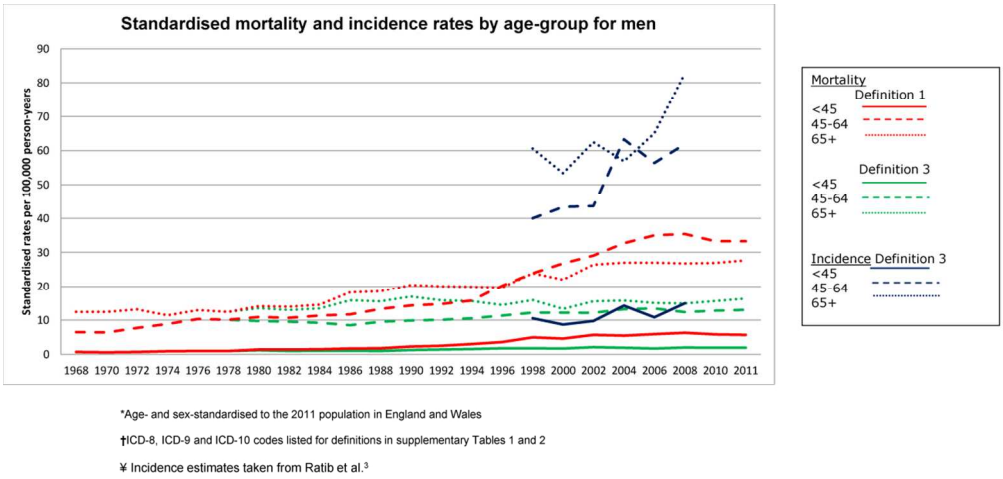
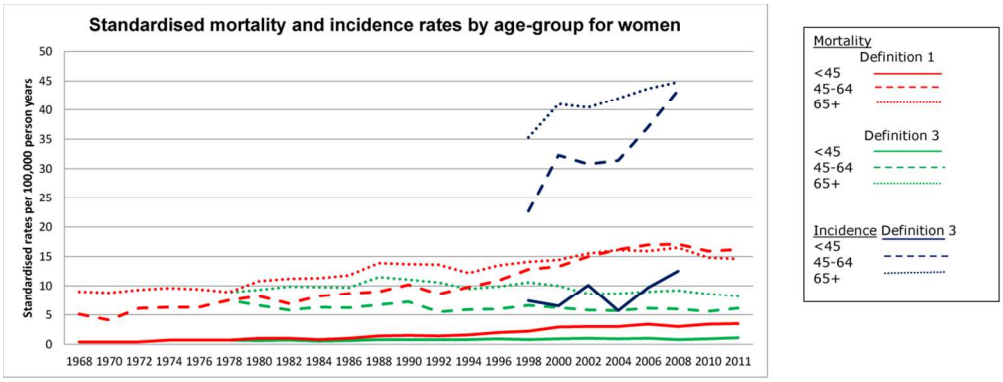


Figure 2 Standardised* mortality and incidence¥ rates by age-group in men, according to cirrhosis definitions 1 and 3†

109x52mm (300 x 300 DPI)



*Age- and sex-standardised to the 2011 population in England and Wales

†ICD-8, ICD-9 and ICD-10 codes listed for definitions in supplementary Tables 1 and 2

¥ Incidence estimates taken from Ratib et al.[3]

Figure 3 Standardised* mortality and incidence¥ rates by age-group in women, according to cirrhosis definitions 1 and 3†

109x53mm (300 x 300 DPI)

Supplementary Table 1 ICD -8 and ICD- 9 codes for liver disease and the three definitions of liver cirrhosis (LC)

ICD version	Code	Description	Liver disease	LC Definition 1†	LC Definition 2§	LC Definition 3¥
ICD-8	5700	Acute/subacute necrosis of liver	Yes	No	No	No
	5710	Cirrhosis of liver-alc	Yes	Yes	Yes	Yes
	5719	Cirrhosis of liver-othe	Yes	Yes	Yes	Yes
	5720	Supperative hepatitis and liver abscess	Yes	No	No	No
	5730	Other disease of liver	Yes	No	No	No
ICD-9	570	Acute/subacute necrosis of liver	Yes	No	No	No
	5710	Alcoholic fatty liver	Yes	Yes	No	No
	5711	Acute alcoholic hepatitis	Yes	Yes	No	No
	5712	Alcoholic cirrhosis of liver	Yes	Yes	Yes	Yes
	5713	Alcoholic liver damage, unspec	Yes	Yes	No	No
	5714	Chronic hepatitis	Yes	Yes	No	No
	5715	Cirrhosis of liver without mention of alcohol	Yes	Yes	Yes	Yes
	5716	Biliary cirrhosis	Yes	Yes	No	Yes
	5718	Other chronic nonalcoholic liver disease	Yes	Yes	No	No
	5719	Unspec chronic liver disease without mention of alcohol	Yes	Yes	No	No
	5720	Abscess of liver	Yes	No	No	No
	5721	Portal pyemia	Yes	No	No	No
	5722	Hepatic coma	Yes	No	No	No
	5723	Portal hypertension	Yes	No	No	Yes
	5724	Hepatorenal syndrome	Yes	No	No	No
	5728	Other sequelae of chronic liver disease	Yes	No	No	No
	573	Other disorders of liver	Yes	No	No	No
	4560	Oesophageal varices with bleeding	No	No	No	Yes

4561	Oesophageal varices without bleeding	No	No	No	Yes
4562	Oesophageal varices in diseases classified elsewhere	No	No	No	Yes

†Leon et al.[13] §Jepsen et al.[16]¥ Ratib et al.[3]

Supplementary Table 2 ICD -10 codes for liver disease and the three definitions of liver cirrhosis (LC)

ICD version	Code	Description	Liver disease	LC Definition 1†	LC Definition 2§	LC Definition 3¥
ICD-10	K70.0	Alcoholic fatty liver	Yes	Yes	No	No
	K70.1	Alcoholic hepatitis	Yes	Yes	No	No
	K70.2	Alcoholic fibrosis and sclerosis of liver	Yes	Yes	No	No
	K70.3	Alcoholic cirrhosis of liver	Yes	Yes	Yes	Yes
	K70.4	Alcoholic hepatic failure	Yes	Yes	No	No
	K70.9	Alcoholic liver disease, unspecified	Yes	Yes	No	No
	K71.0	Toxic liver disease with cholestasis	Yes	No	No	No
	K71.1	Toxic liver disease with hepatic necrosis	Yes	No	No	No
	K71.2	Toxic liver disease with acute hepatitis	Yes	No	No	No
	K71.3	Toxic liver disease with chronic persistent hepatitis	Yes	No	No	No
	K71.4	Toxic liver disease with chronic lobular hepatitis	Yes	No	No	No
	K71.5	Toxic liver disease with chronic active hepatitis	Yes	No	No	No
	K71.6	Toxic liver disease with hepatitis, not elsewhere classified	Yes	No	No	No
	K71.7	Toxic liver disease with fibrosis and cirrhosis of liver	Yes	No	No	Yes
	K71.8	Toxic liver disease with disorders of liver	Yes	No	No	No
	K71.9	Toxic liver disease with disorders of liver	Yes	No	No	No
	K72.0	Acute and subacute hepatic failure	Yes	No	No	No
	K72.1	Chronic hepatic failure	Yes	No	No	Yes
	K72.9	Hepatic failure, unspecified	Yes	No	No	No
	K73	Chronic hepatitis, not elsewhere classified	Yes	Yes	No	No

†Leon et al.[13] §Jepsen et al.[16] ¥ Ratib et al.[3] LC=liver cirrhosis

ICD version	Code	Description	Liver disease	LC Defintion2†	LC Defintion2§	LC Defintion3¥
ICD-10	K74.0	Hepatic fibrosis	Yes	Yes	No	No
	K74.1	Hepatic sclerosis	Yes	Yes	No	No
	K74.2	Hepatic fibrosis with hepatic sclerosis	Yes	Yes	No	No
	K74.3	Primary Biliary cirrhosis	Yes	Yes	No	No
	K74.4	Secondary biliary cirrhosis	Yes	Yes	No	Yes
	K74.5	Biliary cirrhosis, unspecified	Yes	Yes	No	Yes
	K74.6	Other and unspecified cirrhosis of liver	Yes	Yes	Yes	Yes
	K75	Other inflammatory liver diseases	Yes	No	No	No
	K76.0	Other diseases of liver	Yes	No	No	No
	K76.1	Chronic passive congestion of liver	Yes	No	No	No
	K67.2	Central haemorrhagic necosis of liver	Yes	No	No	No
	K76.3	Infarction of liver	Yes	No	No	No
	K76.4	Peliosis hepatis	Yes	No	No	No
	K76.5	Hepatic veno-occlusive disease	Yes	No	No	No
	K76.6	Portal hypertension	Yes	No	No	Yes
	K76.7	Hepatorenal syndrome	Yes	No	No	No
	K76.8	Other specified diseases of liver	Yes	No	No	No
	K76.9	Liver disease, unspecified	Yes	No	No	No
	K77	Liver disorders in diseases classified elsewhere	Yes	No	No	No
	I85.0	Oesophageal varices with bleeding	No	No	No	Yes
	I85.9	Oesophageal varices without bleeding	No	No	No	Yes
	I86.4	Gastric varices	No	No	No	Yes
	I98.2	Oesophageal varices in diseases classified elsewhere	No	No	No	Yes

†Leon et al.[13] §Jepsen et al.[16] ¥ Ratib et al.[3] LC=liver cirrhosis

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
(Title and abstract	1	*(a)* Indicate the study's design with a commonly used term in the title or the abstract p.1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found p.2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported p.4
Objectives	3	State specific objectives, including any prespecified hypotheses p.5
Methods		
Study design	4	Present key elements of study design early in the paper p.6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection p.6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up p.6 *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable p.6/7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group p.6
Bias	9	Describe any efforts to address potential sources of bias p.7
Study size	10	Explain how the study size was arrived at N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why p.7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding p.7
		(*b*) Describe any methods used to examine subgroups and interactions p.7
		(*c*) Explain how missing data were addressed N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed N/A *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses N/A

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed N/A
		(b) Give reasons for non-participation at each stage N/A
		(c) Consider use of a flow diagram N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders N/A
		(b) Indicate number of participants with missing data for each variable of interest N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time p.8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included p.8
		(*b*) Report category boundaries when continuous variables were categorized p.7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses p.10
Discussion		
Key results	18	Summarise key results with reference to study objectives p.11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias p.11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence p.12
Generalisability	21	Discuss the generalisability (external validity) of the study results p.11/13
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based p.18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.