

Otete, Harmony Erobohene (2016) OPPORTUNITIES
IN UK PRIMARY AND SECONDARY HEALTHCARE
SETTINGS TO PREVENT ALCOHOL MISUSE. PhD
thesis, University of Nottingham.

Access from the University of Nottingham repository:

http://eprints.nottingham.ac.uk/33060/1/Thesis_Otetefinal%28corrections%29.pdf

Copyright and reuse:

The Nottingham ePrints service makes this work by researchers of the University of Nottingham available open access under the following conditions.

This article is made available under the University of Nottingham End User licence and may be reused according to the conditions of the licence. For more details see:
http://eprints.nottingham.ac.uk/end_user_agreement.pdf

A note on versions:

The version presented here may differ from the published version or from the version of record. If you wish to cite this item you are advised to consult the publisher's version. Please see the repository url above for details on accessing the published version and note that access may require a subscription.

For more information, please contact eprints@nottingham.ac.uk



The University of
Nottingham

OPPORTUNITIES IN UK PRIMARY AND
SECONDARY HEALTHCARE SETTINGS TO
PREVENT ALCOHOL MISUSE

Eroboghene Harmony Otete

BPharm(Hons), MPH

Thesis submitted to the University of Nottingham
for the degree of Doctor of Philosophy

October 2015

Abstract

Background Alcohol-related deaths and hospital admissions have risen steeply in the United Kingdom and little is known about whether there are opportunities for preventive interventions or opportunities for the earlier detection of alcohol misuse. The purpose of this research was to investigate and describe patterns of healthcare utilisation in the pre-diagnosis period of alcoholic cirrhosis and alcoholic psychosis, two alcohol-related disorders which contribute significantly to alcohol related morbidity and mortality. This information is important as it could greatly facilitate a better understanding of opportunities for the earlier detection of alcohol misuse, and could also potentially encourage and assist practitioners in the timely identification of those who are at high risk of developing significant alcohol-related illnesses.

Specific research objectives

- 1) To estimate rates of primary and secondary healthcare contacts before the diagnosis of alcoholic cirrhosis/psychosis and assess whether this differs from rates in the general population
- 2) To characterise the healthcare contacts and establish whether such consultations were for other conditions known to be related to alcohol.
- 3) As a secondary objective, to establish whether prior healthcare contacts led to recognition of alcohol problems and consequent interventions.

Methods UK general practice and hospital admissions data were used for this research. A population of patients diagnosed with alcoholic cirrhosis and subsequently, a population of patients with alcoholic psychosis were identified. For each case, 10

patients without the disease who were of similar age and from the same general practice were selected as controls. For each disease group, a case-control study design was used to compare rates of primary care contacts and hospital admissions in cases to that of the control population. Further, the reasons for primary care visits and hospital admissions were assessed to describe the frequency of other alcohol-attributable morbidities in cases and controls, and to assess whether there were any morbidities which were strongly associated with the later development of alcoholic cirrhosis and psychosis. Finally, the proportions of patients who had a record of their alcohol use status or a record of an offer of brief alcohol intervention/referral were estimated.

Results

Alcoholic cirrhosis

2,479 patients with alcoholic cirrhosis and 24,790 controls matched on age and GP practice were available for analysis. Assessment of healthcare utilisation showed that people with alcoholic cirrhosis had 50% higher rate of GP visits and twice as many hospital admissions compared to the control population. This excess healthcare use was apparent as far as 10 years pre-diagnosis of alcoholic cirrhosis, but greater excesses were seen within 5 years of diagnosis. Cases of alcoholic cirrhosis did have a higher frequency of other conditions that are partly alcohol-attributable, especially diabetes, epileptic seizures, hypertensive diseases, injuries and digestive diseases. Of all these conditions, injuries, seizures and digestive diseases had the strongest association with the development of alcoholic cirrhosis. Overall, a high proportion of patients with alcoholic cirrhosis (84%) had their alcohol use documented on an average of 4 years before diagnosis and 58% of these records indicated harmful/hazardous drinking. However, only 1 in 5 patients (22%) had any record of a brief alcohol intervention or an alcohol referral.

Alcoholic psychosis

1,731 patients with alcoholic psychosis and 17,310 matched controls were included in the study. As with alcoholic cirrhosis, there was a substantially higher rate of primary and secondary care use in cases which was apparent up to 10 years prior to disease diagnosis. Cases of alcoholic psychosis also had a higher frequency of partly alcohol attributable morbidities. However, the strongest associations were seen for intentional and unintentional injuries and seizures. 78% of cases of alcoholic psychosis did have their alcohol use recorded, 50% had a harmful/hazardous drinking record but only 1 in 5 (19%) had any intervention record.

Conclusion and Implications: This research has shown that patients who misuse alcohol make frequent contacts with both primary and secondary care, suggesting that there are high number of opportunities within these healthcare settings to improve the early identification and treatment of alcohol use. Relatively few patients were identified to have received brief alcohol interventions/referral despite the large proportion of people with documented drinking problems, suggesting potential inadequacy in the treatment of alcohol problems. However, this may also partly be an artefact of recording biases. Considering that alcohol is one of the leading preventable causes of morbidity and mortality in the UK, these findings should encourage healthcare professionals to, at the very least, screen for alcohol misuse in patients presenting with any alcohol-attributable condition, and for policy makers to consider directing more effort towards integrating alcohol screening and brief intervention into routine clinical practice.

Publications and presentations

Peer reviewed publications from thesis

- Otete HE, Orton E, West J, Fleming KM. Sex and age differences in the early identification and treatment of alcohol use: a population based study of patients with alcoholic cirrhosis. *Addiction*. 2015; Aug 1. doi: 10.1111/add.13081
- Otete HE, Orton E, Fleming KM, West J. Alcohol-attributable health care attendances up to 10 years prior to diagnosis of alcoholic cirrhosis: a population based case control study. *Liver International* 2015 Nov 12. doi: 10.1111/liv.13002.

Conference presentations (Oral)

- Otete HE, Orton E, West J, Fleming KM. High number of opportunities in primary and secondary care to prevent alcohol induced cirrhosis. United European Gastroenterology (UEG) conference, 2015.
- Otete HE, Orton E, West J, Fleming KM. Missed opportunities to provide interventions for patients with alcohol problems: a retrospective study on individuals with alcoholic cirrhosis. International Network on Brief interventions for Alcohol and other drugs Conference, 2014.
- Otete HE, Orton E, West J, Fleming KM. Opportunities to prevent harmful or hazardous alcohol consumption in UK primary healthcare settings: a study of individuals with a diagnosis of alcohol-induced cirrhosis. Alcohol Research UK Annual conference, 2014.
- Otete HE, Orton E, West J, Fleming KM. Opportunities to prevent alcohol misuse in Primary healthcare settings: a study of individuals with a diagnosis of Alcohol-induced cirrhosis. Trent Regional Society for Academic Primary Care conference, 2014.

Conference presentations (Poster)

- Otete HE, Orton E, West J, Fleming KM. Opportunities to prevent alcohol misuse in UK primary healthcare settings: a retrospective study of individuals with a diagnosis of alcohol-induced cirrhosis. *Journal of Epidemiology & Community Health* 2014;68 (Suppl 1):A47-A48
- Otete HE, Orton E, Fleming KM, West J. Alcohol-attributable healthcare attendances in patients with alcoholic cirrhosis. Trent Regional Society for Academic Primary Care conference, 2015.

Acknowledgements

The research presented in this thesis has been funded by the University of Nottingham Vice-Chancellor's Scholarship for Research Excellence. Additional financial support was received from the UK Centre for Tobacco and Alcohol Control Studies and Professor Joe West's Senior Clinical Research fellowship and is gratefully acknowledged.

I would like to sincerely thank my supervisors- Dr Kate Fleming, Professor Joe West and Dr Elizabeth Orton- for giving me the opportunity to do this research. Your support, encouragement and guidance throughout the entire period were unquestionably invaluable; I absolutely enjoyed the entire research experience and I have so far learnt so many new academic and non-academic skills from you that will help me progress in my career and beyond. Thank you.

I would also like to thank both the past and present B121 and B126 team- especially Alyshah, Caz, Ruth, Lu, Sonia, Nafeesa and Beade for your valuable methodological help and other general non-academic advice and support. It has been wonderful being amongst you all and you all made the research experience pleasant.

Finally, I am eternally grateful to God, my parents, the rest of my family and my friends - I was only able to do all that I did because of your unending support, love and confidence in me.

Table of contents

Abstract.....	2
Publications and presentations	5
Acknowledgements.....	7
Table of contents	8
List of Tables	15
List of Figures	18
List of Abbreviations	20
1 Introduction	21
1.1 Guidelines and terminologies	22
1.2 Global trends in drinking behaviour	25
1.3 Trends in drinking behaviour in the UK.	29
1.3.1 Data sources.....	29
1.3.2 Country-wide consumption based on sales data.....	33
1.3.3 Prevalence of at-risk drinking in the UK.....	34
1.4 Alcohol and health: the scale of the UK problem	35
1.4.1 Sex variation in alcohol related ill-health	38
1.4.2 Socio-economic variation in alcohol related ill-health	38
1.4.3 Age variations in alcohol related ill-health	39
1.4.4 Socio-economic costs of alcohol use in the UK.....	39
1.5 Alcoholic cirrhosis	41
1.5.1 Definition	41
1.5.2 UK burden of alcoholic cirrhosis	41
1.5.3 Drinking threshold for cirrhosis	42

1.5.4	Disease progression and survival.....	43
1.5.5	Lack of information on cirrhosis prevention.....	44
1.5.6	Previous research on opportunities to prevent alcoholic cirrhosis	45
1.6	Alcoholic psychosis	47
1.6.1	Definition	47
1.6.2	Burden of alcoholic psychosis in the UK	47
1.6.3	Drinking threshold for alcoholic psychosis	48
1.6.4	Disease progression and survival in alcoholic psychosis	49
1.6.5	Treatment of alcoholic psychosis.....	50
1.6.6	Lack of information on alcoholic psychosis prevention.....	50
1.7	Alcohol harm reduction interventions.....	52
1.7.1	Population level approaches.....	53
1.7.2	Screening and brief interventions.....	55
1.7.3	Acceptability and implementation of screening and brief interventions.....	66
1.7.4	Other interventions for alcohol misuse that can be offered following screening.....	68
1.8	Summary and Justification of thesis	70
1.9	Thesis aims and objectives.....	71
1.9.1	Outline of thesis chapters	72
2	Description of study data.....	73
2.1	Introduction to Clinical Practice Research Datalink (CPRD).....	73
2.1.1	Data Validity	74
2.1.2	Data coding	74
2.1.3	Data format of the CPRD.....	75
2.2	Hospital Episode Statistics (HES) data.....	77
2.2.1	Data format.....	77
2.3	Data Linkage.....	80
2.4	Justification of using CPRD	81

2.4.1	Relevant data	81
2.4.2	Size	81
2.4.3	Representativeness.....	82
2.4.4	Prospectively collected data	82
2.4.5	Data validity	82
2.4.6	Incomplete recording.....	83
2.4.7	Gaps in alcohol consumption data.....	84
2.4.8	Duration of follow up	84
2.5	Summary of data strengths and limitations	85
2.6	Ethical approval, anonymity and data management.....	85
3	Building the thesis datasets	86
3.1	Definition of the alcoholic cirrhosis population.....	86
3.1.1	Patient selection	86
3.1.2	Date of diagnosis.....	88
3.1.3	Inclusion and exclusion criteria.....	88
3.1.4	Selection of control population	88
3.2	Defining the alcoholic psychosis study population.....	90
3.2.1	Datasets	90
3.2.2	Patient selection	90
3.2.3	Date of diagnosis.....	93
3.2.4	Inclusion and exclusion criteria.....	93
3.2.5	Control selection	93
3.3	Identifying evidence to substantiate the codes used for selecting the alcoholic psychosis population.	94
3.3.1	Patient grouping.....	94
3.3.2	Identifying supporting evidence	94
3.3.3	Results.....	97
3.3.4	Overall summary	106

3.4	Defining study outcomes	107
3.4.1	Primary care consultations	107
3.4.2	Hospital admissions	108
3.4.3	Alcohol records	108
3.5	Definition of covariates	110
3.5.1	Age	110
3.5.2	Smoking status	111
4	Healthcare utilisation and recording of alcohol status and interventions prior to alcoholic cirrhosis diagnosis	112
4.1	Introduction	112
4.1.1	Background	112
4.2	Methods	114
4.2.1	Study population	114
4.2.2	Observation period	114
4.2.3	Study variables	115
4.2.4	Other variables	115
4.2.5	Statistical analyses	116
4.3	Results	118
4.3.1	Population characteristics	120
4.3.2	General practice consultations before diagnosis	122
4.3.3	Hospital admissions before diagnosis	125
4.3.4	Alcohol use records	128
4.3.5	Alcohol use interventions	133
4.4	Discussion and interpretation	136
4.4.1	Main findings	136
4.4.2	Strengths and limitations	137
4.4.3	Comparison with previous studies	139
4.4.4	Implications	139

4.4.5	Conclusions	141
5	Alcohol attributable morbidities present in patients before the diagnosis of alcoholic cirrhosis.....	143
5.1	Introduction	143
5.2	Methods.....	144
5.2.1	Dataset and study population.....	144
5.2.2	Identifying partly alcohol-attributable morbidity in primary and secondary care	145
5.2.3	Covariates	146
5.2.4	Statistical analysis	146
5.3	Results.....	149
5.3.1	Population characteristics.....	149
5.3.2	Alcohol-attributable healthcare attendances.....	151
5.4	Discussion and Interpretation.....	163
5.4.1	Main findings	163
5.4.2	Study strengths and limitations	164
5.4.3	Comparison with previous literature	166
5.4.4	Conclusion and implications	166
6	Healthcare utilisation and recording of alcohol status and interventions in men and women prior to alcoholic psychosis.....	169
6.1	Methods.....	169
6.1.1	Study population.....	169
6.1.2	Observation period	170
6.1.3	Outcomes	170
6.1.4	Statistical analysis	171
6.2	Results.....	173
6.2.1	Study population characteristics.....	173
6.2.2	Use of primary healthcare prior to the diagnosis of alcoholic psychosis	175

6.2.3	Use of hospital services.....	178
6.2.4	Alcohol use screening/recording	181
6.2.5	Records of alcohol intervention.....	187
6.3	Discussion and interpretation.....	190
6.3.1	Summary of findings	190
6.3.2	Strengths and limitations	190
6.3.3	Implications for clinical practice	192
6.3.4	Chapter conclusions.....	193
7	Alcohol-attributable morbidities present in patients before the diagnosis of alcoholic psychosis.....	195
7.1	Introduction	195
7.2	Methods.....	195
7.2.1	Data.....	195
7.2.2	Population.....	195
7.2.3	Observation period	195
7.2.4	Identifying partly alcohol-attributable morbidity in primary and secondary care	196
7.2.5	Covariates	196
7.2.6	Missing data	196
7.2.7	Statistical analysis	196
7.3	Results.....	198
7.3.1	Alcohol attributable healthcare attendances	200
7.4	Discussion and Interpretation.....	214
7.4.1	Summary of findings	214
7.4.2	Strengths and limitations	214
7.4.3	Interpretation in the context of other studies.....	216
7.4.4	Chapter conclusions and implications	217
8	Thesis summary, conclusions and recommendations for future research.....	218

8.1	Summary	218
8.2	Thesis strengths	220
8.3	Issues identified	222
8.4	Implications for clinical practice	225
8.5	Implications for future research	232
8.5.1	Using patients with other alcohol related diseases to answer similar research questions.....	232
8.5.2	Additional data and methods	232
8.5.3	Practice-level research.....	233
8.5.4	Potential for risk prediction modelling	234
8.5.5	Economic modelling studies	234
8.5.6	Other outcomes	235
8.5.7	Conclusions	236
	References	237
	Appendices.....	255
	Appendix 1: Brief description of alcohol attributable fractions and estimating of alcohol related harm.....	255
	Appendix 2: Code list used to identify supportive evidence for incident cases of alcoholic psychosis identified in only CPRD data.....	257
	Appendix 3: Code list used to identify supportive evidence for incident cases of alcoholic psychosis identified in HES data.	259
	Appendix 4: Code list for medications considered as supporting evidence for incident cases of alcoholic psychosis	265
	Appendix 5: Code list for alcohol related outcomes.....	268
	Appendix 6: Code list for smoking	274
	Appendix 7: Addiction journal publication	276

List of Tables

Table 1-1	Summary of available data sources to measure drinking behaviour in the UK	30
Table 1-2	Alcohol attributable diseases and corresponding ICD-10 codes	36
Table 2-1	File structure of the data files in CPRD	76
Table 2-2	File structure of the data file contained in HES	79
Table 3-1	Read and ICD-10 codes for Alcoholic cirrhosis.....	87
Table 3-2	Read and ICD-10 codes for alcoholic psychosis based on the broad and restrictive definitions.....	92
Table 3-3	Description of the population of alcoholic psychosis identified using two case definitions.....	98
Table 3-4	Number of cases identified by each definition, stratified into the three patient groups.	99
Table 3-5	Cases of alcoholic psychosis with supporting evidence.....	102
Table 3-6	Cases of alcoholic psychosis with definition 2 who have supporting evidence.....	105
Table 4-1	Basic characteristics of cases of alcoholic cirrhosis and the control population	121
Table 4-2	Overall and yearly primary care consultation rates and rate ratios of cases of alcoholic cirrhosis and controls	124
Table 4-3	Overall and yearly admission rates (per 10 person years) and rate ratios of cases of alcoholic cirrhosis and controls	127
Table 4-4	Proportion of patients who had any alcohol use record during the pre-diagnosis/ pseudo-diagnosis period.	129
Table 4-5	Time between earliest record of alcohol use and alcoholic cirrhosis diagnosis/pseudo-diagnosis	130
Table 4-6	Timing between earliest harmful/hazardous record and disease diagnosis or pseudo-diagnosis.....	131
Table 4-7	Proportion of patients with any alcohol use record stratified by sex and age with OR and 95 CIs	132

Table 4-8	Proportion of patients with any record of alcohol brief intervention or referral for specialist treatment during the pre-diagnosis/pseudo-diagnosis period.....	134
Table 4-9	Proportion of patients with any alcohol intervention record stratified by sex and age and OR and 95% CIs	135
Table 5-1	Baseline characteristics of the study population.....	150
Table 5-2	Proportion of patients with at least one partially alcohol-attributable condition at any point during the study, with OR (95% CI) comparing cases to controls.	152
Table 5-3	Proportion of patients with at least one partially alcohol-attributable condition at any point during the study, with OR (95% CI) comparing cases to controls, stratified by sex and age.....	154
Table 5-4	Overall and age stratified proportions and odds ratios for selected comorbidities (classified by ICD 10 headings) for cases and controls.....	156
Table 5-5	Proportions and ORs for all morbidities for cases and controls	159
Table 5-6	The proportion of patients presenting with each examined condition at different periods before cirrhosis diagnosis with OR (95% CI) comparing cases to controls.....	161
Table 6-1	Baseline demographics of cases of alcoholic psychosis and controls matched by age and GP practice	174
Table 6-2	Overall and yearly primary care consultation rates and rate ratios of cases of alcoholic psychosis and controls.....	176
Table 6-3	Overall and yearly admission rates and rate ratios of cases of alcoholic psychosis and controls.....	179
Table 6-4	Proportion of patients with any record of alcohol use.....	182
Table 6-5	Time between earliest alcohol use record and diagnosis of alcoholic psychosis or pseudo-diagnosis among those with a record of alcohol use	183
Table 6-6	Timing between harmful or hazardous drinking record and alcoholic psychosis diagnosis/pseudo-diagnosis among those with a record of harmful or hazardous drinking	184
Table 6-7	Proportion of patients with any alcohol use record stratified by sex and age and OR and 95% CIs	186

Table 6-8	Proportion of patients with any record of brief alcohol intervention and alcohol related referral.....	188
Table 6-9	Proportion and OR (95% CIs) of patients with any alcohol intervention record, stratified by age.	189
Table 7-1	Characteristics of the study population.	199
Table 7-2	Proportions of patients with at least one partially alcohol-attributable condition at any point during the study, with OR (95% CI) comparing cases to controls.	201
Table 7-3	Proportion of patients with at least one partially alcohol- attributable condition at any point during the study, with OR (95% CI) comparing cases to controls, stratified by sex and age.....	203
Table 7-4	Prevalence of partly alcohol attributable conditions by ICD-10 group	205
Table 7-5	Proportions by ICD-10 group stratified by age.	207
Table 7-6	Proportions and ORs for each morbidity for cases and controls.....	210
Table 7-7	The proportion of patients presenting with each examined condition at different periods before psychosis diagnosis with OR (95% CI) comparing cases to controls.....	212

List of Figures

Figure 1-1	Five year change in recorded alcohol per capita consumption, 2006-2010	26
Figure 1-2	Prevalence of heavy episodic drinking among current drinkers (%), 2010.....	28
Figure 1-3	Per-capita consumption of pure alcohol in the UK 1990-2012(British Beer and Pub Association, 2015)	33
Figure 1-4	Alcohol treatment and intervention options available in the U	52
Figure 1-5	Pathway for Screening and brief intervention delivery recommended by NICE	57
Figure 1-6	The Alcohol Use Disorder Identification Test (AUDIT) full version	59
Figure 1-7	The trans-theoretical model of change by Prochaska and DiClemente	62
Figure 3-1	Summary of the process used in identifying evidence to substantiate the diagnosis of alcoholic psychosis	96
Figure 3-2	Alcohol use records available in CPRD	109
Figure 4-1	Selection of the patient population.....	119
Figure 4-2	Yearly primary care consultation rates per person-year prior to alcoholic cirrhosis diagnosis	123
Figure 4-3	Yearly hospital admission rates per 10 person-years prior to alcoholic cirrhosis diagnosis.	126
Figure 5-1	Adjusted odds ratios for each alcohol-attributable disease, stratified by age	157
Figure 5-2	Adjusted Odds ratios for each alcohol-attributable morbidity, stratified by time to diagnosis	162
Figure 6-1	Yearly primary care consultation rates per person-year prior to alcoholic psychosis	177
Figure 6-2	Yearly hospital admission rates per 10 person-years prior to alcoholic psychosis diagnosis.....	180
Figure 7-1	Adjusted Odds ratios for alcohol attributable morbidities, stratified by age.....	208

Figure 7-2	Adjusted odds ratios for each alcohol attributable morbidity, stratified by time	213
------------	--	-----

List of Abbreviations

AAF	Alcohol-attributable fractions
ABI	Alcohol brief interventions
A&E	Accident and Emergency
AUDIT	Alcohol Use Disorders Identification Test
CMO	Chief Medical Officer
CI	Confidence Interval
CPRD	Clinical Practice Research Datalink
DALY	Disability Adjusted Life Years
DH	Department of Health
DSM	Diagnostic and Statistical Manual of Mental disorders
GLF	General Lifestyle Survey
GP	General Practitioners
HES	Hospital Episodes Statistics
ICD	International Classification of Diseases
LRT	Likelihood Ratio Test
MHRA	Medicines & Healthcare products Regulatory Agency
MUP	Minimum Unit Pricing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OPN	Opinions and Lifestyle Survey
ONS	Office for National Statistics
OR	Odds Ratio
SBI	Screening and brief interventions
UTS	“up-to-standard”
UK	United Kingdom
WHO	World health Organization

Chapter 1

1 Introduction

Alcohol is a leading cause of preventable death and morbidity among adults and young people in both low and high income countries, killing about 3.3 million people globally every year. Through its toxic and dependence producing properties, it increases the risk of over 200 health problems (1–3). These range from chronic conditions such as cancers, mental health disorders, and liver disease which can affect drinkers after many years of alcohol abuse, to acute injuries such as traffic accidents, falls, and suicide, which are potentially fatal and can cause disability at a relatively young age (4–6). In 2004, an estimated 76.3 million people worldwide could be diagnosed with alcohol use disorders and a total of 58.3 million life years were lost due to alcohol(7). In Europe alone, about 55,000 people aged 15-29 died as a result of their heavy drinking. This burden is not equally distributed between EU member states, and the UK is among the major contributors to this death toll. Between 2012 and 2013 in the UK, at least 8000 people were killed by alcohol specific diseases. In general, over one in four (22%) of deaths in men and one in six deaths (15%) in women aged 35-44 years old in UK are attributable to alcohol consumption(7–9).

The problems associated with alcohol use are far-reaching and not limited to health or to the drinker alone. For example, drinking during pregnancy has been shown to cause developmental impairment to the foetus (10). In wider society(i.e. beyond health), intoxication and dependence has been associated with crime (11,12), domestic violence , child abuse (13,14), risky sexual behaviour (15) and workplace problems, such as absenteeism and lowered productivity (16). In addition, there are also substantial financial implications of both the health and social consequences of alcohol

misuse on the economy. In Europe for example, in 2010, it was estimated that approximately £155.8 million was lost as a result of alcohol through increasing healthcare costs, crime and lowered productivity (17).

The detrimental effects of alcohol have been shown to depend on the amount of alcohol consumed and the pattern of drinking and some studies suggest that light drinking may in fact have beneficial effects on diabetes and ischaemic heart disease(18), resulting in the J shaped curve. It is important to emphasize, however, that these potential positive effects apply to only post-menopausal women and men over 40 years(19). Additionally, given that the comparison group in most of the studies reporting the J shaped effect comprise of both life-time abstainers and ex-drinkers, there is some evidence to suggest that the “sick-quitter effect” where by some people quit drinking due to health reasons, may account for the higher risk observed in the “abstaining group” compared to light drinkers(20,21). Notwithstanding these concerns, it is still true that if any such potential protective properties exist, it is far outweighed by the negative effects of alcohol on disease and injury(1).

1.1 Guidelines and terminologies

Underpinning attempts to reduce alcohol related risks are recommendations of what should constitute the “safe” level at which alcohol can be consumed. The lower risk guidelines in the UK recommend that men and women should not drink more than 21 and 14 units of alcohol per week respectively. In terms of daily drinking, it is advisable that men should not drink more than 3-4 units of alcohol per day and women not more than 2-3 units a day. It is also advisable that after a bout of heavy drinking, individuals should have at least a 48 hr alcohol free period.

Drinking above these limits substantially increases the risk of future harm and there are several terminologies used to describe drinking above low risk guidelines:

Hazardous drinking or increasing-risk drinking: this refers to individuals drinking between 22 and 50 units per week for men, and between 15 and 35 units per week for women but with no evidence of harm present (2,7,22).

Harmful drinking or higher risk drinking: refers to drinking above the recommended limits with evidence of alcohol related harm or specifically drinking above 50 units per week for men and above 35 units per week for women (7,22).

Binge drinking: is defined in England as drinking more than twice the recommended daily limits i.e. more than 8 units in one day for men or more than 6 units for women (23). Sometimes, the alternative term “heavy episodic drinking” is used to refer to this pattern of drinking (24).

Dependent drinking: is at the far end of the drinking spectrum and is defined as a strong desire or compulsion to use alcohol which is accompanied by difficulties to control drinking, tolerance to increasing levels of consumption and withdrawal in the absence of alcohol (2,25). The WHO recognises dependent drinking as a mental disorder and it is included in key disease classification tools such as the International classification of Diseases (ICD-10) and the Diagnostic and Statistical Manual of Mental disorders (DSM-V).

While these guidelines are useful to help the public minimise their risk of future harm, it is important to emphasize that they are based on evidence from the 1987 Royal College of physicians’ report *‘The medical consequences of alcohol abuse; a great and growing evil’*(8). Therefore, as acknowledged in the recent House of Commons Science and Technology Committee report, it remains the case that an update of these guidelines would be beneficial. For example, there is the need for guidelines that

reflect new epidemiological evidence which suggest the risk of certain cancers increase even at levels as low as 1 unit of alcohol per day. Additionally, guidelines that provide clearer and more specific evidence-based recommendations for population subgroups would be relevant, given that subgroups of the population have varying predispositions to harm at different levels of drinking e.g. the young versus the elderly (26).

1.2 Global trends in drinking behaviour

Historically, there are two separate but related dimensions of alcohol consumption which have been identified as being significant to public health (27). First, the **total amount** of alcohol consumed over time, which is linked to increases in the risk of chronic disease outcomes (28). Second, the **pattern** with which alcohol is consumed in particular heavy episodic or binge drinking, which impacts the more acute consequences of alcohol such as injury and violence (28,29). According to WHO, although the total volume of alcohol consumed globally has been stable in the last decade (Figure 1-1), there has been an increase in harmful patterns of drinking in different countries and regions around the globe (27,30). Europe in particular ranks as the heaviest drinking region in world (30,31). Measured using sales data, WHO estimated consumption of pure alcohol among those 15 years and older who drank in Europe in 2011 to be 10 litres of pure alcohol per year, nearly double the world average of 6 litres and considerably higher than many other regions of the world such as Africa, Southeast Asia (16,27). This regional average however hides large differences between countries in the European region. For example, southern European countries such as Cyprus, Greece and Italy and Nordic countries such as Iceland and Sweden have relatively low levels of consumption and in most of these countries alcohol per capita consumption has fallen since 1980s (32). Whereas, consumption levels in countries such as Russia, Ireland and the UK as at 2011 were up to 50% higher than what they were two decades ago (27).

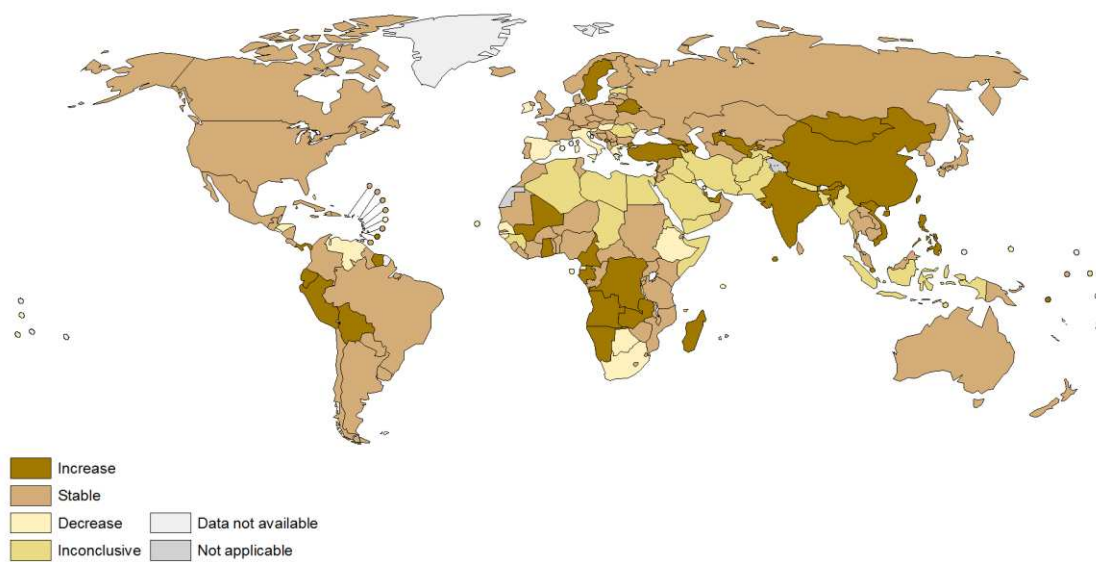
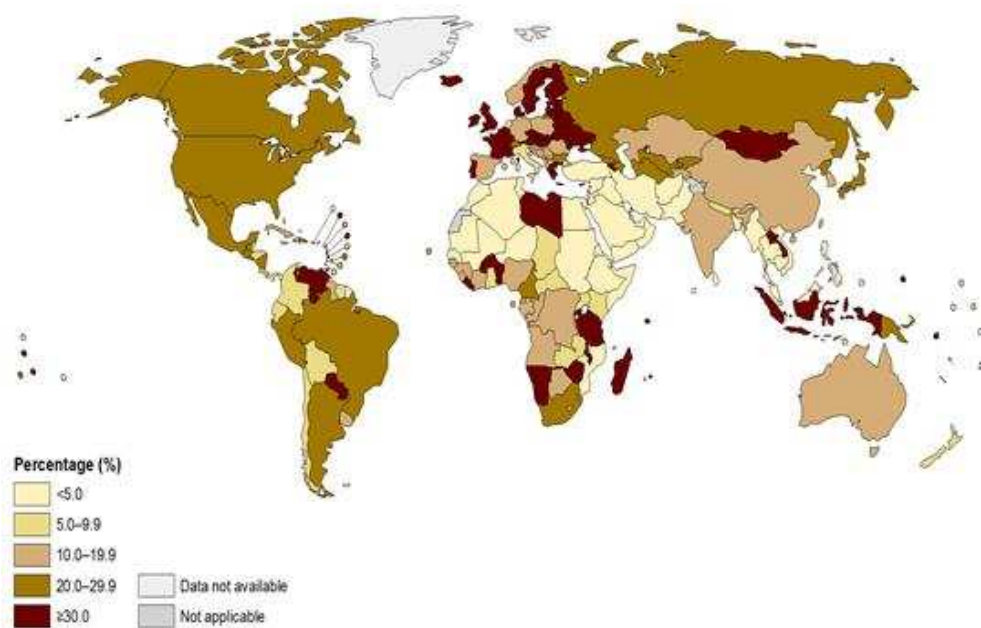


Figure 1-1 Five year change in recorded alcohol per capita consumption, 2006-2010

In terms of the prevalence of harmful drinking, it is estimated that today, approximately 16% of the world's drinking population (approximately 200 million people) drink at harmful and hazardous levels, compared to 11% in 2005 (7). Specific areas across the globe where the most rapid rise in harmful consumption patterns have been seen are in Asia and Africa, and a number of factors have been suggested as contributing to these increases including the availability and accessibility of unlicensed locally made alcohol which is very difficult to control(33). Across the rest of the world, areas with high numbers of those who engage in heavy drinking include the UK, Russia, Ukraine, Ireland, Denmark, and Australia (Figure 1-2). More young people in particular, in these countries drink heavily than those in the USA, France, and other Mediterranean countries. So, for example, in 2010 28% of UK 15-year-olds acknowledged binged drinking in the past 30 days whereas in the USA, the corresponding proportion was 17% (34).

Figure 1-2 **Prevalence of heavy episodic drinking among current drinkers (%), 2010**



1.3 Trends in drinking behaviour in the UK.

1.3.1 Data sources

Currently, alcohol consumption in the UK is monitored by several data sources. In addition to sales data, which enables comparison of UK consumption with other countries, social surveys which measure drinking patterns in cross-sections of the population are also available. Table 1-1 summarizes the drinking measures that can be obtained in each data source, alongside the merits and potential limitations of each.

Table 1-1 Summary of available data sources to measure drinking behaviour in the UK

Data source	Background	Years of available data	Drinking measures	Estimating units of alcohol consumption from self-reported drinking habits	Merits and Limitations
Opinions and Lifestyle Survey(OPN) formerly known as General lifestyle Survey (GLF) (35)	National survey conducted annually since 1971, on a sample of approximately 20,000 individuals in UK.	Alcohol information available every year from 1971 onwards, except for breaks in 1997-1998 when the survey was reviewed, and 1999-2000 when the survey was redeveloped	Reports two measures of consumption for respondents: maximum amount drunk on any one day in the previous seven days before survey Average weekly consumption.	Up until 2006: a half pint of normal-strength beer, lager or cider, a single measure of spirits, a glass of wine, or a small glass of sherry or other fortified wine were classified as being equivalent to 1 UNIT of alcohol from 2006 unit measurement was revised due to changes in the average pub glass size and increasing strength of drinks: a glass of wine, half pint or small can strong beer (adults only) were classified as 2 units; while the small can normal-strength beer or alcopop = 1.5 units	Merits: Provides information on individual drinking patterns. Useful to estimate the prevalence of various patterns of alcohol misuse Takes into account home produced/smuggled alcohol Limitations: Self-reported measures of alcohol consumption are often underestimates of the true drinking levels of individuals.
The Health Survey for England (HSE)(36)	National survey conducted annually since 1991 on UK adults and children living in private	Alcohol information available every year from 1991 onwards	Reports one measure of consumption for respondents: maximum amount of alcohol consumed on	From 1991 to 2005 same as GHS a half pint of normal-strength beer, lager or cider, a single measure of spirits, a glass of wine, or a small glass of sherry or	Same as GLF Additional limitation Contains 20 years less data as

	households		heaviest drinking day in the last week	other fortified wine, small bottle or can alcopops= 1 unit of alcohol Updated conversion from 2006 just as GHS.	compared to GLF Does not report weekly consumption
British Beer and Pub Association	Based on tax paid alcohol sales	Information available from 1900		Converts volume of beer, cider, spirits, wine and alcopops sold in UK population to per capita (litres per head per year) consumption	Merit: Provides information on country level consumption Limitation: Cannot be used to explore individual drinking patterns. Likely to underestimate country level consumption because it does not include home produced, imported alcohol or duty free alcohol.

Data from repeated cross-sectional population surveys provide a very valuable resource for identifying the type of people who are drinking and for examining prevalence and trends of various drinking patterns (e.g. Harmful drinking, binge drinking). However due to intentional or unintentional under-reporting of drinkers or low-response rates of survey participants, these surveys substantially underestimate consumption levels (37). As such, they are considered unsuitable for estimating the total volume of consumption at the country level. Sales data on the other hand, rely on data from country-wide sales and taxation which captures most of the alcohol sold and imported into country. Although it may not account for smuggled or homemade alcohol it is considered more robust, compared to surveys, for estimating the total volume of alcohol consumed by the entire population (37).

1.3.2 Country-wide consumption based on sales data

Figure 1-3 summarises the long term trends in alcohol consumption in the UK based on sales data from the British Beer and Pub association-BBPA, 2015.

In the beginning of the 20th century, alcohol consumption in the UK increased for many years, from approximately 9 litres for every person aged 15 years and older in 1990 to a peak of 11.6 litres in 2004. After this peak in 2004, however, there began a slow decline in consumption and the most recent 2012 figure suggests that consumption has reduced by 18% since the peak in 2004. Overall, there has been a change in the beverage preference in the UK since the early 1990s. In recent years more potent alcohol drinks such as spirits and wine have increasingly become common, a trend believed to be partly driven by an increase in rates of drinking at home (38).

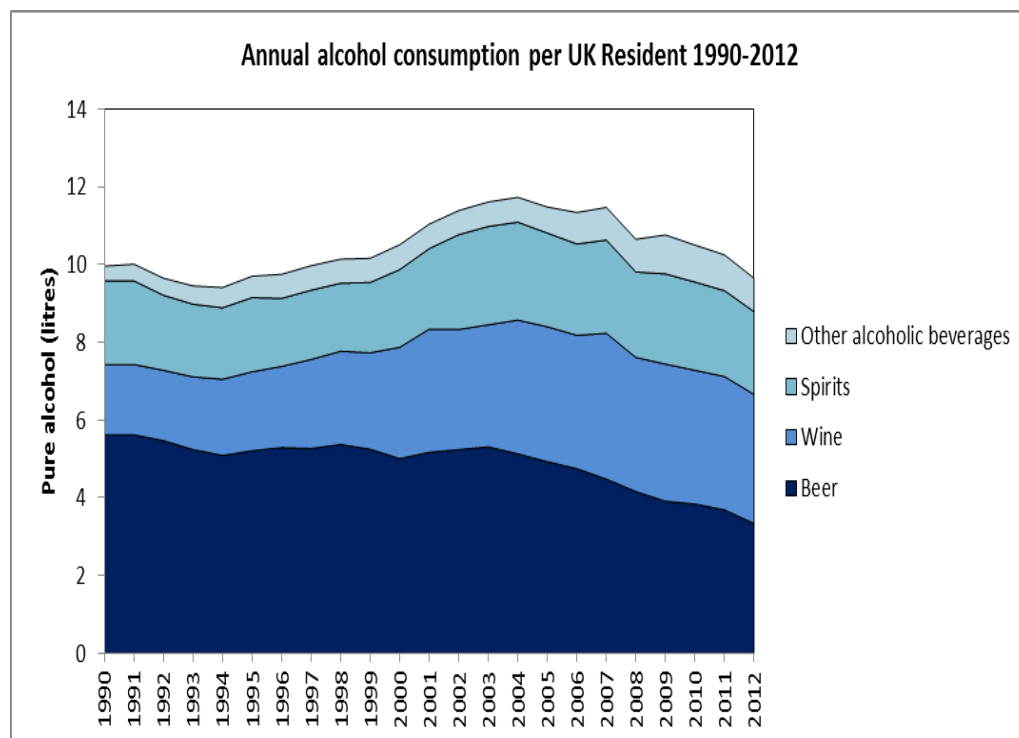


Figure 1-3 Per-capita consumption of pure alcohol in the UK 1990-2012(British Beer and Pub Association, 2015)

While there are several known factors which may have driven the increase in alcohol consumption between the early 1990's and 2000s (e.g. increased access, affordability and availability, a rise in the UK's economy, and more sophisticated alcohol marketing (39)), the recent downward trend in consumption is less clear although some attribute it to the 2008 UK financial crisis. Despite this recent moderation however, the consumption level in the UK is way above the world average of 6 litres and there is still a high prevalence of high-risk drinking behaviour in the UK. The general household survey provides a summary of high risk drinking patterns in the UK.

1.3.3 Prevalence of at-risk drinking in the UK

Data obtained from the General household survey, the standard reference point for individual drinking patterns, shows that approximately 10 million people in the UK drink at levels which can be categorised as at-risk drinking. This includes one in three men (34%) and one in five women (26%) who are hazardous drinkers, another 6% of men and 2% of women who are harmful drinkers, and a total of 1.6 million men and women who already show signs of alcohol dependence(40). Given that people knowingly or unknowingly underestimate the amounts they drink in self-reported surveys these prevalence figures are probably conservative estimates.

Overall high risk drinking in the UK is more common among younger age groups, but gradually there has been an overall downward trend in binge drinking prevalence in the 16 to 24 year olds since 2005 (41,42). Across socio-economic groups, high risk drinking is more prevalent amongst those in non-manual compared to manual groups,

with estimates of current hazardous drinking at 38% in professional groups and 32% in manual groups (41).

1.4 Alcohol and health: the scale of the UK problem

The health effects of alcohol use have been known for many years with some diseases being classed as being 100% attributable to alcohol for e.g. alcoholic liver disease, alcoholic hepatitis, and others, as partially attributable to alcohol e.g. diabetes, oesophageal cancer, injuries. Table 1-2 shows a list of both wholly and partly alcohol attributable conditions. Appendix 1 contains some details on how attributable fractions are calculated and applied to estimate the scale of alcohol related problems in the UK.

In 2012/2013, alcohol related diseases and injuries accounted for an estimated 1.2 million NHS hospital admissions, representing 6% of all NHS admissions and a 139% increase since 2001 when alcohol attributable admissions were estimated at just over 400,000(23,43). According to the Office for National Statistics (ONS), alcohol also caused 6,490 deaths in the same period(43).

Table 1-2 Alcohol attributable diseases and corresponding ICD-10 codes

	Disease/Related health problem	ICD-10*
Wholly attributable conditions	Alcohol-induced pseudo-Cushing's syndrome	E24.4
	Mental and behavioural disorders due to use of alcohol	F10
	Degeneration of nervous system due to alcohol	G31.2
	Alcoholic polyneuropathy	G62.1
	Alcoholic myopathy	G72.1
	Alcoholic cardiomyopathy	I42.6
	Alcoholic gastritis	K29.2
	Alcoholic liver disease	K70
	Chronic pancreatitis (alcohol induced)	K86.0
	Ethanol poisoning	T51.0
	Methanol poisoning	T51.1
	Toxic effect of alcohol, unspecified	T51.9
	Accidental poisoning by and exposure to alcohol	X45
Partially attributable conditions	Malignant neoplasm of lip, oral cavity and pharynx	C00-C14
	Malignant neoplasm of oesophagus	C15
	Malignant neoplasm of colon	C18
	Malignant neoplasm of rectum	C20
	Malignant neoplasm of liver and intrahepatic bile ducts	C22
	Malignant neoplasm of larynx	C32
	Malignant neoplasm of breast	C50
	Epilepsy and Status epilepticus	G40-G41
	Hypertensive diseases	I10-I15
	Cardiac arrhythmias	I47-I48
	Heart failure	I50-I51
	Haemorrhagic stroke	I60-I62,I69.0-I69.2
	Ischaemic stroke	I63-I66,I69.3-I69.4
	Oesophageal varices	I85
	Gastro-oesophageal laceration-haemorrhage syndrome	K22.6
	Liver cirrhosis	K73, K74
	Acute and chronic pancreatitis	K85, K86.1
	Psoriasis	L40 excluding L40.5
	Spontaneous abortion	O03

	Road traffic accidents (Death)	§
	Road traffic accidents (Hospital admission)	
	Pedestrian traffic accidents(Death)	§§
	Pedestrian traffic accidents (Hospital admission)	
	Water transport accidents	V90-V94
	Air/space transport accidents	V95-V97
	Fall injuries	W00-W19
	Work/machine injuries	W24-W31
	Firearm injuries	W32-W34
	Drowning	W65-W74
	Inhalation of gastric contents/Inhalation and ingestion of food causing obstruction of the respiratory tract	W78-W79
	Fire injuries	X00-X09
	Accidental excessive cold	X31
	Intentional self-harm/Event of undetermined intent	X60-X84, Y10-Y34
	Assault	X85-Y09
	Diabetes mellitus	E11
	Ischaemic heart disease	I20-I25
	Cholelithiasis	K80

**ICD-10 International Statistical Classification of Disease, a medical classification by the World health Organization.*

Overall, the major contributors to alcohol related morbidity and mortality in the UK are liver disease and mental and behavioural disorders. Mental and behavioural disorders accounted for two-thirds of all alcohol-specific admissions (198,600) in 2012/13 while alcoholic liver disease accounted for 50,510 admissions(43). In terms of mortality, alcoholic liver disease accounted for at least 63% (n=4,425) of all alcohol-specific deaths based on ONS data(44).

1.4.1 Sex variation in alcohol related ill-health

In most developed countries like the UK, alcohol problems generally tend to be higher among adult men than women and this correlates with evidence that men are more likely to engage in risky drinking behaviours (7,45). The 2012 figures show that 66% (n=4,232) of all alcohol related deaths and 65% of all alcohol-related admissions (~650,000) in England were in men. However, this trend appears to be reversed among the younger age groups where in 2012, 55% of alcohol related admissions were in females (38). One potential explanation for the trend in younger age-group could be differences in informal thresholds of admissions between boys and girls, where by boys are more likely to be released to go home whereas girls are more likely to be kept for overnight monitoring.

1.4.2 Socio-economic variation in alcohol related ill-health

Variations in alcohol related harm across socio-economic groups are reflected in mortality rates, as people from socio-economic disadvantaged neighbourhoods in UK are 2 times more likely to die from any alcohol related condition compared to the least

deprived. They are also 3 times more likely to die from specific chronic effects of drinking like alcoholic cirrhosis (43,44,46,47). This however, is often referred to as the alcohol harm paradox. The paradox comes from the fact that, as described earlier, people from lower socio-economic classes are reported to consume less alcohol. In a study evaluating potential explanations for the lower alcohol related harm among people with higher socio-economic status despite their higher levels of consumption, it was suggested that perhaps, differential access to health services in more deprived areas, a clustering of protective risk factors in affluent neighbourhoods or a disproportionate underestimation of alcohol consumption in lower socio-economic groups may account for this paradox(47).

1.4.3 Age variations in alcohol related ill-health

Absolute mortality and hospitalization rates are highest in older people (38,44), however, the younger compared to the old in the UK are disproportionately affected by alcohol related harm. Several studies have found that specific diseases such as cirrhosis affect younger populations. This trend was initially highlighted in 2001 by the Chief Medical Officer's report for England and also in 2012, and is most likely attributable to the high prevalence of heavy episodic/binge drinking in the younger age groups, which increases the risk for most chronic diseases (48,49).

1.4.4 Socio-economic costs of alcohol use in the UK.

In addition to all the health harms mentioned above, a huge socio-economic burden is caused by alcohol in the UK. This burden includes both direct and indirect health and social costs (27). Direct costs include all costs related to inpatient and out-patient care

for alcohol-related illnesses and costs to the justice sector through crime, vehicle crashes and violence. Indirect costs capture premature death, unemployment and productivity losses due to absenteeism from work.

In 2008, it was estimated that alcohol related disorders cost the NHS £2.7 billion for hospital admissions, primary care consultations, attendance at Accident and Emergency (A&E) services and prescriptions for alcohol treatments (50,51). More recent Figures using 2013 data however put these health related costs in England at £3.5 billion per annum. In terms of other costs, in England alone, violent accidents and drink driving accidents in 2012 cost the justice system over £11 billion (52). Workplace losses due to alcohol have also been estimated to cost £6.4 billion through absenteeism and lowered productivity (5). Overall, the Cabinet Office and the National Social Marketing Centre put the total cost of alcohol related harm in the UK at between £21 and £55 billion annually (50,53). This however, doesn't include intangible costs that result from the suffering and reduced quality of life borne by the drinkers and their families.

The studies contained within this thesis focus on two wholly alcohol attributable conditions which stand out as having the most significant morbidity and mortality impact of alcohol use, namely alcoholic cirrhosis and alcoholic psychosis. Discussed below is the existing knowledge of the epidemiology, healthcare burden and potential for prevention of these two conditions.

1.5 Alcoholic cirrhosis

1.5.1 Definition

Alcoholic cirrhosis is a chronic degenerative disease of the liver in which normal liver tissues are replaced with scars (fibrosis) and nodules due to repetitive injury from long-term heavy drinking (54,55). It is considered the final clinical pathway of alcohol related liver injury and evolves from milder/reversible stages of alcoholic liver disease namely: steatosis (the accumulation of fat deposits in the liver caused by changes in lipid metabolism due to heavy alcohol consumption) and alcoholic hepatitis (the inflammation/swelling of the liver due to injury from heavy drinking). Currently, the possibility of reversal of alcoholic cirrhosis has been suggested (56), however in most cases, the damage to the liver in alcoholic cirrhosis is irreversible and eventually results in liver failure, especially in the presence of continuous drinking (54,55).

1.5.2 UK burden of alcoholic cirrhosis

Over the past 30 years, and as highlighted by several reports by the Chief Medical Officer for England, the burden of cirrhosis in the UK has increased. This increase is in

stark contrast to the decreasing trend seen in other large neighbouring European countries (49,57,58).

One mortality study conducted in 2006, estimates that cirrhosis mortality rates increased by 69% between 1990 and 2001 in the UK (57). In a more recent incidence study in 2012, the incidence of cirrhosis in the UK was found to have increased by over 57% from 24.6 in 1998 to 38.4 per 100,000 person-years in 2009 (59). To put this burden in context, the increase in the incidence of cirrhosis in the UK is greater than that of the top four most commonly diagnosed cancers in the UK namely breast, lung, prostate and bowel cancers (59).

In 2012, the Office for National statistics figures showed that approximately 20% of all alcohol related liver deaths were due to cirrhosis (1,384 deaths). Whilst these numbers were much lower than the death toll of other chronic diseases like cancers and respiratory disease, alcoholic cirrhosis particularly kills people at a relatively younger age making it more problematic. Approximately 90% of all people who die from cirrhosis in the UK are under 70 years old and people as young as 25 years old in the UK have been diagnosed with the disease (60). Therefore in terms of years of life lost, liver cirrhosis is much more prominent.

1.5.3 Drinking threshold for cirrhosis

Studies assessing the amount of alcohol which can result in cirrhosis suggest that there is a dose-response relationship between alcohol intake and cirrhosis development. However, the exact amount of alcohol required to cause cirrhosis remains unknown. In most studies, consumption levels of between 24g (4 units) and 80g (~10units) of alcohol per day have been reported as the threshold for increasing risk of cirrhosis morbidity and mortality(61–66). For example, in a large cohort study of mortality risk

among 6,152 Danish subjects, Kamper-jorgensen et al found that compared to the general population, men and women drinking more than 5 drinks a day (60g of alcohol) had a 27-fold and 35-fold increased mortality from alcoholic cirrhosis (62). In another study looking at morbidity risk, men and women who exceeded 40-60grams(5-7 units) and 20-40grams(~2-4units) of alcohol daily respectively for over 10 years were found to have a higher relative risk of developing cirrhosis than non-drinkers (61).

Regarding drinking patterns, previous studies have shown that daily drinking is associated with a higher risk of cirrhosis than infrequent drinking. Regarding beverage type, there is the suggestion that wine is associated with a lower risk of cirrhosis compared to spirits and beer, but this association was only true for men as the study authors report a lack of statistical power to confirm the same trend in women (67).

1.5.4 Disease progression and survival

Alcoholic cirrhosis tends to develop slowly, often without symptoms in the early stages (compensated cirrhosis), until it progresses rapidly to a decompensated phase which is marked by various complications such as ascites (the build-up of fluid in the abdomen), portal hypertension (high blood pressure in the portal vein) and oesophageal varices (dilation of the veins in the lower oesophagus which often results in oesophageal bleeding) (68). It is often at this decompensated phase which is marked by poor prognosis that most patients are identified(68–70). For some of these patients, there is no recovery from chronic cirrhosis and death follows within a short period of time; for example the median survival for those with ascites has been estimated at 6 months (71). However, for some other patients, survival may improve if complete abstinence from alcohol is achieved. For example Verrill et al found a 7 year survival of 72% for patients with cirrhosis who became abstinent after diagnosis compared to 44% in

patients who continued to drink. Although given the small size of this study (100 patients) and that abstinence was measured at only 30 days after diagnosis of alcoholic cirrhosis it is possible that this finding was due to chance (72).

Notably, comorbidities play an important role in the prognosis of people with cirrhosis. In 2015, one cohort study found that over 40% of deaths in alcoholic liver disease were from non-liver related causes and these findings were similar to a much earlier study in 2003 which found 49% of deaths in people with cirrhosis did not have cirrhosis as the underlying cause of death(73,74). Further data supporting the effect of comorbidity on mortality in cirrhosis was recently provided in the review by Jepsen (69). In this review, it was reported that cardiovascular diseases (e.g. myocardial infarction, cardiac arrhythmia, and cardiomyopathy), epilepsy, metastatic cancer, chronic kidney disease, peptic ulcer, venous thromboembolism and lung disease, if present among patients, led to an increased mortality. The exact extent to which these individual comorbidities are present in patients is still yet to be comprehensively described. This information could help not only in the management of those with the disease but also in the early identification of those who are at risk or those still at an early stage in the disease course. For this reason, a part of this thesis specifically investigates the extent of specific alcohol related morbidities that occur in patients prior to cirrhosis diagnosis.

1.5.5 Lack of information on cirrhosis prevention

In principle, alcoholic cirrhosis is preventable and there is encouraging evidence (discussed in a subsequent section) that early identification strategies which can identify and help at-risk drinkers to reduce their drinking can protect against alcohol related problems like cirrhosis. Even in those who have already been diagnosed with

the disease, there is evidence to show that abstinence from alcohol which may be achieved through the use of brief interventions could potentially improve survival (75–79). For example in one of the earliest studies reporting this potential positive effect of abstinence after disease diagnosis, Saunders et al found that 5 year survival in patients with compensated cirrhosis more than doubled in patients who could achieve abstinence from alcohol(75). Improvements in survival were also seen in those with decompensated cirrhosis although this was only after abstinence had been maintained for a whole year after diagnosis (75).

The rising rates of cirrhosis mortality in the UK therefore raises questions about whether there are opportunities, in practice, to deliver preventive interventions to those at risk of the disease and to what extent interventions are currently being delivered.

1.5.6 Previous research on opportunities to prevent alcoholic cirrhosis

Two studies have attempted to address the issue of opportunities for intervening in people with cirrhosis by describing the clinical activity of patients in the time before they were diagnosed with or die from the disease. But they have been small, unrepresentative and subject to multiple biases including selection and recall bias.

In the first study for instance, 94 hospitalised patients diagnosed with cirrhosis between 1995 and 2000 were investigated. In addition to reviewing the medical notes of patients to identify any previous morbidity, 45 patients were randomly selected and asked to recall their contacts with health services during the 5 years pre-diagnosis i.e. how often they had been admitted to hospital or been to their GP. The authors reported that 33% of patients had been previously admitted to hospital an average of three times for an alcohol-related condition and among the 45 who were interviewed,

the mean number of previous GP visits during the period under review ranged from 2 - 13 visits per year(80).

In the second study which was conducted in Scotland UK, the authors avoided recall bias by examining patients' medical notes for evidence of previous healthcare utilisation. However, the study population was also small (65 cases) and comprised of only people who had died from alcoholic liver disease suggesting that the study population is unrepresentative of the wider population of patients with alcoholic cirrhosis. The findings of this study however showed that both GP and hospital admissions for other alcohol related problems (reported in terms of mean lifetime consultation rate) were common (5-24 consultations over the patient's life time) prior to the time patients died from alcoholic liver disease(81).

Despite the said limitations, these two studies provide the best available evidence of healthcare utilisation and morbidities in patients prior to alcoholic cirrhosis diagnosis and suggest that there may be opportunities for earlier detection. Therefore in general, contemporary understanding of opportunities for preventing cirrhosis remains limited and a large study investigating prior hospital admissions and GP visits in a comprehensive cohort of patients with alcoholic cirrhosis is therefore clearly required.

1.6 Alcoholic psychosis

1.6.1 Definition

Alcohol-related psychosis is a severe mental disorder that occurs in people who drink heavily (82). It manifests as prominent verbal or visual hallucinations and delusions, and is sometimes accompanied with suicidal tendencies and aggression (83,84). Though the disease was previously thought to have a favourable prognosis (85,86), a recent study found high rates of re-hospitalization among 60% of patients with the disease to suggest that the disease course may in fact be less favourable than what has been previously reported(84).

1.6.2 Burden of alcoholic psychosis in the UK

Specific estimates of deaths and hospital admissions for alcoholic psychosis are not available, hence looking at the burden of alcohol related mental disorders in general provides the best estimate of the disease related morbidity and mortality.

In the past 10 years in the UK, there has been an increasing healthcare burden of alcohol related mental problems, psychosis included (87). As mentioned in section 1.3, alcohol related mental problems account for the highest number of alcohol specific hospital admissions in England. Using data from Hospital Episodes Statistics, which contains details of all admissions at NHS hospitals, it was estimated that there were just under 200,000 admissions for alcohol related mental problems in 2012, representing more than double the number of admissions that were recorded in 1995-6.

Most of the burden caused by alcoholic psychosis is likely to arise from the high risk of suicide and high rates of comorbidity among patients. In terms of suicide, it is estimated that there is a 60% increased risk of suicide within the first year of psychosis diagnosis(88). In terms of comorbidity, in 2010, Perala et al looked at comorbidities in a sample of 39 patients identified with alcoholic psychosis from the Finnish national register. They found a high rate of psychiatric comorbidity among patients, whereby 76% out of 38 patients had other mental disorders such as depression and anxiety. In addition, a high rate of alcohol-related comorbidities was also found as 91% of cases had previously received hospital treatment for either head injury, fractures, liver disease, gastritis, and arrhythmias, compared to 2% in the control population (84). Since the study oversampled patients over 80 years in a ratio of 2:1, the very high rate of comorbidity identified may not be surprising but might in turn represent an overestimate of the true rate of comorbidity in a more age-representative population. To date, there appear to be no other studies describing comorbidities in patients with alcoholic psychosis in the UK.

1.6.3 Drinking threshold for alcoholic psychosis

Although it is known that alcoholic psychosis is precipitated by chronic alcoholism, there is a lack of contemporary information about the specific amount of alcohol or the duration of heavy drinking that can precipitate the disorder. The only study that could be found, that provides some information of duration and volume of drinking associated with psychosis, dates back to 1998. In this study by George et al, drinking history was obtained from 34 patients of Asian descent (30 Indians, 3 Chinese and 1 Malay) who had been diagnosed with alcoholic psychosis. Based on data from each patient, the authors estimated that patients had a mean duration of 14 years of heavy

drinking (range 10 years to 25 years) and consumed on average 69.5 units of alcohol weekly, prior to the diagnosis of the disease (89). Since this was self-reported and sometimes based on a patient's family member recall, there is likely to be some element of information bias due to recall which would mean that the estimated average consumption volume may be lower than what it actually is.

1.6.4 Disease progression and survival in alcoholic psychosis

As early as 1989, Glass et al reviewed the available evidence on the natural history of alcoholic psychosis which at the time was referred to as alcoholic hallucinosis. The systematic review identified 6 studies conducted between 1952 and 1978 in several countries (Switzerland, England, Australia, United States and Denmark). The number of patients across studies ranged from 33 to 113 and patients were followed up for between 6 to 10 years from the first episode of psychosis, although there were cases followed up for one year and some for up to 41 years. All studies defined alcoholic hallucinosis based on the presence of a history of heavy drinking and auditory hallucinations, which is similar to criteria recommended by the DSM-V today.

Across all studies, a favourable prognosis was reported with initial episodes of alcoholic psychosis lasting for less than 6 months. However a relapsing course of the disease was reported among 5% - 30% of patients.

Soyka et al recently found a high rehospitalisation rate of between 62%-68% among patients with alcoholic psychosis suggesting a more chronic disease course. However, in Soyka's study the authors failed to report the reason why patients were rehospitalised making it unclear whether rehospitalisation was for alcoholic psychosis relapse or for any other comorbid disease that was present among patients.

Generally as alcoholic psychosis correlates with alcoholism, there are a cluster of factors which may result in higher negative outcomes among patients (90). For example, comorbidity with psychiatric complications such as depression, anxiety may result in suicide. In addition, comorbidity with cardiovascular or alcohol related liver disease could also worsen prognosis. Some of the other complications reported from studies outside the UK that may be comorbid with alcohol-related psychosis include liver disease, diabetes mellitus, injury, hypertension, and cerebrovascular disease, all of which are associated with significant morbidity(91).

1.6.5 Treatment of alcoholic psychosis

There are no clear guidelines for the treatment of alcoholic psychosis. A number of studies on the disease suggest that abstinence from alcohol could lead to the resolution of symptoms however, there have been cases where psychosis was found to persist even with no alcohol consumption(85). In terms of specific pharmacotherapy, antipsychotic medication is frequently recommended for patients and a combination of these medications with abstinence has been shown to have favourable outcomes although these have been in uncontrolled case reports (92).

1.6.6 Lack of information on alcoholic psychosis prevention

Since there are no clear treatments for alcoholic psychosis despite its morbidity burden, identification of patients at risk of developing the disease may be the only way of reducing disease burden. There is some evidence on preventing alcohol related disorders in general which suggest people at risk of alcoholic psychosis may benefit from abstinence or a reducing in levels of drinking since the disease is believed to be

100% alcohol-attributable. Unfortunately, as with cirrhosis and other chronic alcohol related diseases, there is little information in the UK on admissions, healthcare use, and GP visits during the time before people are diagnosed with alcoholic psychosis, or any information on physical comorbidities that could help in the earlier identification of people who are at risk of the disease. Contemporary information on these outcomes is therefore needed in order to inform and better understand potential opportunities for preventing alcoholic psychosis.

1.7 Alcohol harm reduction interventions

There are several interventions that could potentially be used to reduce alcohol related harms. Since the early 2000s, the Department of health and other independent experts in the UK have published several guidelines on these interventions (5,22,93–95). The interventions range from population level approaches that directly or indirectly reduce the availability of, and demand for alcohol, to more specialised clinical treatments aimed at treating those with severe drinking problems and dependence. Figure 1-4 below shows the main intervention options currently recommended. As this thesis is focused on understanding if there are opportunities for preventive clinical interventions, this section would focus more on brief interventions, its design, effectiveness and knowledge gaps. However, before describing the screening and brief intervention strategy in detail, population level approaches to reducing alcohol related harm are briefly summarised below.

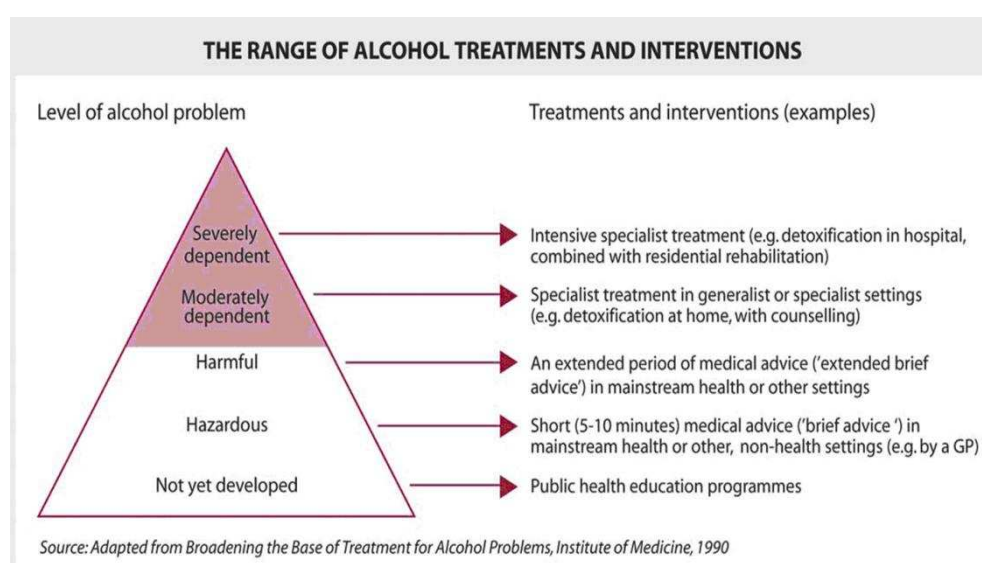


Figure 1-4 Alcohol treatment and intervention options available in the UK

1.7.1 Population level approaches

1.7.1.1 Pricing measures

One population level approach to reduce harmful drinking is through alcohol price increases. Price increases aim to reduce the affordability and demand of alcohol and can be achieved either through increased taxation or by setting a minimum unit price (MUP) at which alcohol can be sold. A 10% price increase in alcohol is estimated to result in 4.4% decrease in alcohol consumption(96). Furthermore, several modelling studies have found that increases in alcohol price reduces the rates of alcohol related mortality, road accidents and alcohol dependence (97,98). Currently in the UK, taxes are levied on national and imported alcoholic drinks. MUP however, is still subject of an ongoing debate. Current evidence suggests that setting a MUP of £0.45 could save 2000 lives and over 60,000 hospital admissions over 10years. It could also reduce inequalities as harmful drinkers with the lowest incomes are likely to be affected the most(99). However the argument against is that such high pricing policy would not only affect harmful drinkers but also serve to penalise moderate drinkers(100). Earlier in 2009, the UK government proposed to introduce a minimum unit price of alcohol of £0.50. The government's commitment to this policy was however recently withdrawn citing the above concern.

1.7.1.2 Advertising restrictions

Alcohol advertising rules which regulate where and how alcohol is promoted are also an important means of reducing alcohol consumption (101). Most of these rules are based on epidemiological evidence which show that alcohol advertising influences

people's attitude to drinking (102). Indeed, in a recent study it was found that when the alcohol industry increased their expenditure on alcohol advertising there was a corresponding increase in alcohol consumption (103). The authors of this study however acknowledge that this finding is subject to several biases including failure to control for other factors that influence drinking such as parental or peer influence (103). However, lessons from tobacco control suggest that a link between seeing more advertisements and increased use of a product is plausible. There are currently few advertising bans in place in the UK, an example of which is the prohibition of youth targeted advertising content. But few unpublished reports have shown that these are not well enforced by the advertising standards authority.

1.7.1.3 Others

Other population level policy areas for which there is reasonable supporting evidence includes regulations on drink driving limits, limiting of hours of alcohol sales and monitoring of off-license and on-license alcohol outlet densities(94). Although School-based education programmes are recommended, there is inconclusive evidence as to whether such programmes can effectively lead to sustained changes in drinking behaviour/attitudes among children and young people(104,105).

1.7.2 Screening and brief interventions

As early as 1980 the WHO highlighted the need for efficient methods to identify and treat people with harmful and hazardous levels of alcohol consumption before significant harms become pronounced (106,107). There was a call for strategies that could be implemented with minimum time and resources and within this context “screening and brief interventions” was developed.

Screening is the process whereby healthcare staff can identify at-risk drinkers who can then be subsequently offered or referred on for counselling sessions, known as brief interventions. According to WHO, this strategy is the most cost-effective behavioural intervention and fills the gap between efforts at primary prevention (which are not established in many countries) and more intensive treatments for people with serious alcohol related disorders (108). The rationale behind this strategy and its potential effectiveness is that by intervening early when people are beginning to drink at levels that put their health at risk, healthcare professionals can influence drinking behaviour and reduce the prevalence of problem drinking thereby reducing the associated medical and socio-economic problems (109–111). As indicated on the scale (Figure 1-4), brief interventions are targeted to harmful and hazardous drinkers who form the largest group of problem drinkers. For dependent drinkers, brief interventions are shown to be ineffective and more specialist treatment services are required.

Screening and brief interventions can be used in a range of healthcare settings including primary care, pharmacies, hospital settings and A&E departments. However, the most ideal setting is thought to be primary care given its usual role in delivering preventive work and also due to the high number of patients who visit their GPs every

year(108,112–114). In the UK for example at least 78% of the population visit their GP at least once a year.

There are a wide range of healthcare staff that can perform the screening and intervening process. They include general practitioners (GPs), practice nurses, health visitors, dieticians and more specialist workers such as lifestyle counsellors or alcohol health workers(115). A fairly recent systematic review however suggests that interventions delivered by non-physicians (physician assistants and nurse practitioners) may be less effective than those delivered by physicians(116).

To inform the effective implementation of screening and brief interventions within healthcare settings, several guidance and clinical flow pathways have been written to help practitioners. The Figure (Figure 1-5) below shows the proposed pathway for the delivery of screening and brief interventions in health care settings as described by the National Institute for Health and Care Excellence (NICE) (117).

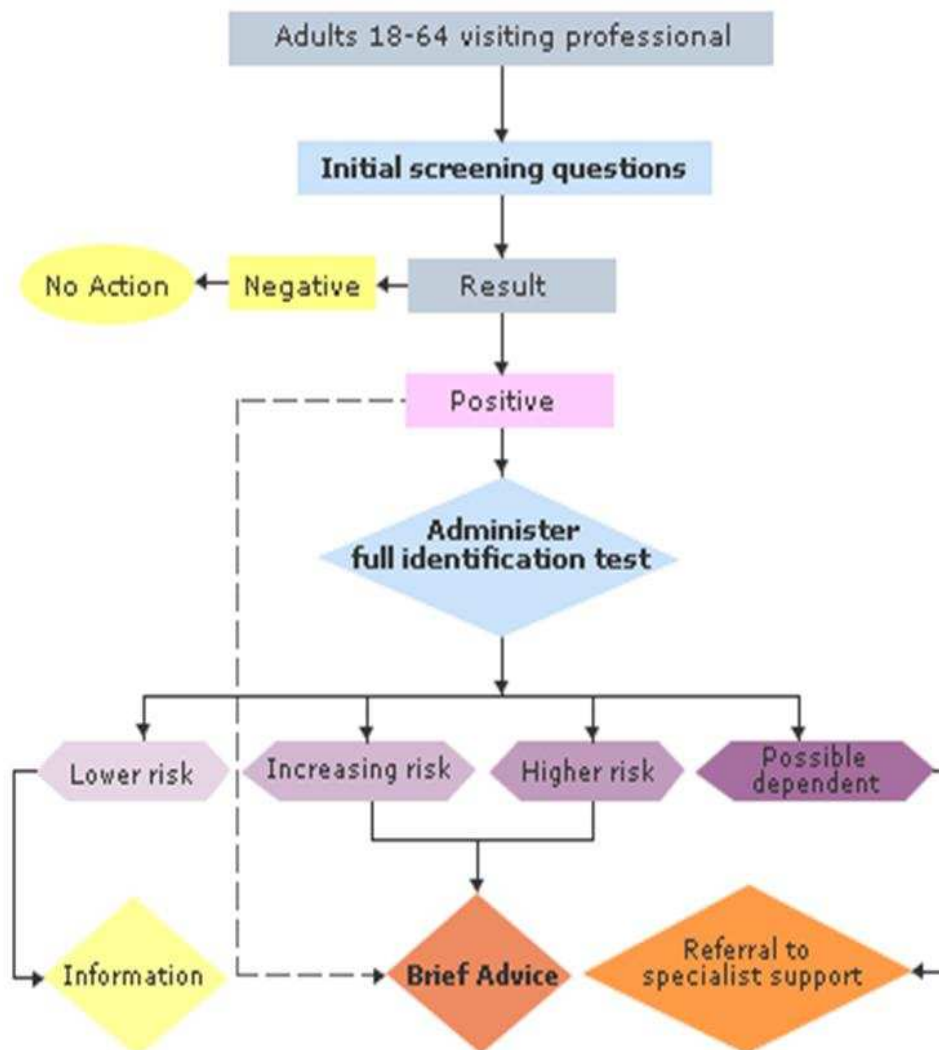


Figure 1-5 Pathway for Screening and brief intervention delivery recommended by NICE

1.7.2.1 Screening in healthcare settings

NICE recommends that healthcare workers should assess the drinking status of adults aged 16 years and over. Opportunities for this assessment include during a patient's registration with a general practice, subsequent health care visits, during routine health checks e.g. the 'NHS health check', hospital admissions, and also during assessments for other behavioural habits e.g. smoking (117).

There are several methods that can be used for this screening, each having varying degrees of precision, invasiveness, and acceptability to practitioners and patients. Standardized questionnaires such as Alcohol Use Disorders Identification Test (AUDIT)(118), Michigan alcohol screening test (MAST) and shorter versions modified to suit healthcare settings faced with time constraints e.g. Fast alcohol screening test (FAST) are however considered the most effective; partly due to their high sensitivity in detecting harmful drinkers, their cost-effectiveness and ease of administration(117–121).

Typically what is expected is that practitioners would administer one of the shortened validated alcohol screening tools such as the AUDIT-C (122)when patients who are at least 16 years old present for health problems or at registration with a new general Practice (94,123). If the patient's initial alcohol test is positive, then the full AUDIT questionnaire is administered to enable the practitioner ascertain the level of the patient's at-risk drinking. If the final test score indicates that they are drinking above the lower-risk drinking guidelines- so, for example an AUDIT score of 8-15 on the audit indicates harmful drinking- practitioners are encouraged to offer brief advice/interventions. For patients identified as showing signs of alcohol dependence (AUDIT score >16), it is envisaged that practitioners would consider further referral to specialist alcohol treatment services(94). Figure 1-6 shows a sample of the full version of the AUDIT including the scoring system.

Figure 1-6 The Alcohol Use Disorder Identification Test (AUDIT) full version

The Alcohol Use Disorders Identification Test: Interview Version Read questions as written. Record answers carefully. Begin the AUDIT by saying "Now I am going to ask you some questions about your use of alcoholic beverages during this past year." Explain what is meant by "alcoholic beverages" by using local examples of beer, wine, vodka, etc. Code answers in terms of "standard drinks". Place the correct answer number in the box at the right.	
1. How often do you have a drink containing alcohol? (0) Never [Skip to Qs 9-10] (1) Monthly or less (2) 2 to 4 times a month (3) 2 to 3 times a week (4) 4 or more times a week	6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily
2. How many drinks containing alcohol do you have on a typical day when you are drinking? (0) 1 or 2 (1) 3 or 4 (2) 5 or 6 (3) 7, 8, or 9 (4) 10 or more	7. How often during the last year have you had a feeling of guilt or remorse after drinking? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily
3. How often do you have six or more drinks on one occasion? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily Skip to Questions 9 and 10 if Total Score for Questions 2 and 3 = 0	8. How often during the last year have you been unable to remember what happened the night before because you had been drinking? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily
4. How often during the last year have you found that you were not able to stop drinking once you had started? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily	9. Have you or someone else been injured as a result of your drinking? (0) No (2) Yes, but not in the last year (4) Yes, during the last year
5. How often during the last year have you failed to do what was normally expected from you because of drinking? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily	10. Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down? (0) No (2) Yes, but not in the last year (4) Yes, during the last year
Record total of specific items here If total is greater than recommended cut-off, consult User's Manual.	

Several studies have tested the sensitivity and specificity of the AUDIT in detecting harmful or hazardous drinkers and in most cases the AUDIT has been found to have not only a high level of sensitivity (ability to genuinely identify heavy drinkers-90-95%) and specificity (ability to exclude false cases-78%), but also to be more sensitive than other questionnaires and invasive biomarker tests. The AUDIT has also performed well in detecting harmful and hazardous drinkers multi-nationally. For example in the WHO collaborative project on the detection of harmful alcohol, the AUDIT had a sensitivity of between 95%-100% in detecting harmful or hazardous drinkers across six countries- Australia, Bulgaria, Kenya, Mexico, Norway and the United States (118). Specificity was also found to be good, although it ranged from as low 66% in the Kenyan population to 89% in Norway(118). Overall, the AUDIT is now considered the “gold-standard” for detecting harmful and hazardous drinkers within primary care settings.

1.7.2.2 Brief interventions

The second essential component of this strategy is the delivery of brief interventions. Brief interventions are defined as time-limited interactions/conversations between a practitioner and patient focused on addressing a harmful behaviour at an early stage and promoting behaviour change before significant future harms develop (108,117).

Originating in the field of smoking cessation, brief interventions rely on motivational interviewing and are grounded on theories of behaviour change which identify that change in behaviour is influenced by an interaction between an individual’s readiness and capacity to change(124). Within the context of alcohol misuse, brief interventions aim to motivate hazardous or harmful drinkers to reflect on their drinking, increase their knowledge about potential risks and reduce their alcohol consumption to safer

levels. The essential components of brief intervention can be summarised by the acronym “FRAMES” which means: Feedback (respectfully giving patient personalised information on the risk from their drinking), Responsibility (stating clearly that the decision to change is the patient’s responsibility), Advice (providing advice to the patient on health and social risks of alcohol use), Menu (offering the patient options for behaviour change), Empathy (responding without judgement), and Self-efficacy (working to increase the patient’s confidence that they can make changes).

Brief interventions may vary in duration and intensity and this is usually dependent on the severity of the patient’s alcohol problem. For example, for hazardous drinkers i.e. patients who exceed recommended drinking limits but have not yet experienced any alcohol related harm, the most basic level of intervention which can consist of two simple statements, in which the consulting physician states their concern about the patients drinking and explains the consequences of such drinking behaviour in 5-10 minutes is appropriate. Whereas for harmful drinkers i.e. patients already experiencing alcohol related harm such as liver disease or diabetes, extended brief interventions generally around 20-30 minutes, over multiple face-to-face sessions may be more appropriate⁽¹¹²⁾.

There is also the suggestion that the content of interventions can vary based on the stage of change that a person is at. Figure 1-7 represents a developed trans-theoretical model explaining the stages of change that may influence the success or failure of attempts to change people’s behaviour. Based on this model, patients could be at any stage ranging from pre-contemplation (where they do not see a problem with their alcohol use and are not considering any change) to recurrence (where they may have changed but then have relapsed back to their old drinking behaviour). Acknowledging

that there are no clear-cut boundaries between stages, it is still suggested that brief interventions should be tailored to the stage an individual appears to be at, and for individuals at an early stage of pre-contemplation or contemplation for instance, providing simple information and feedback that can raise awareness is likely to be more effective.

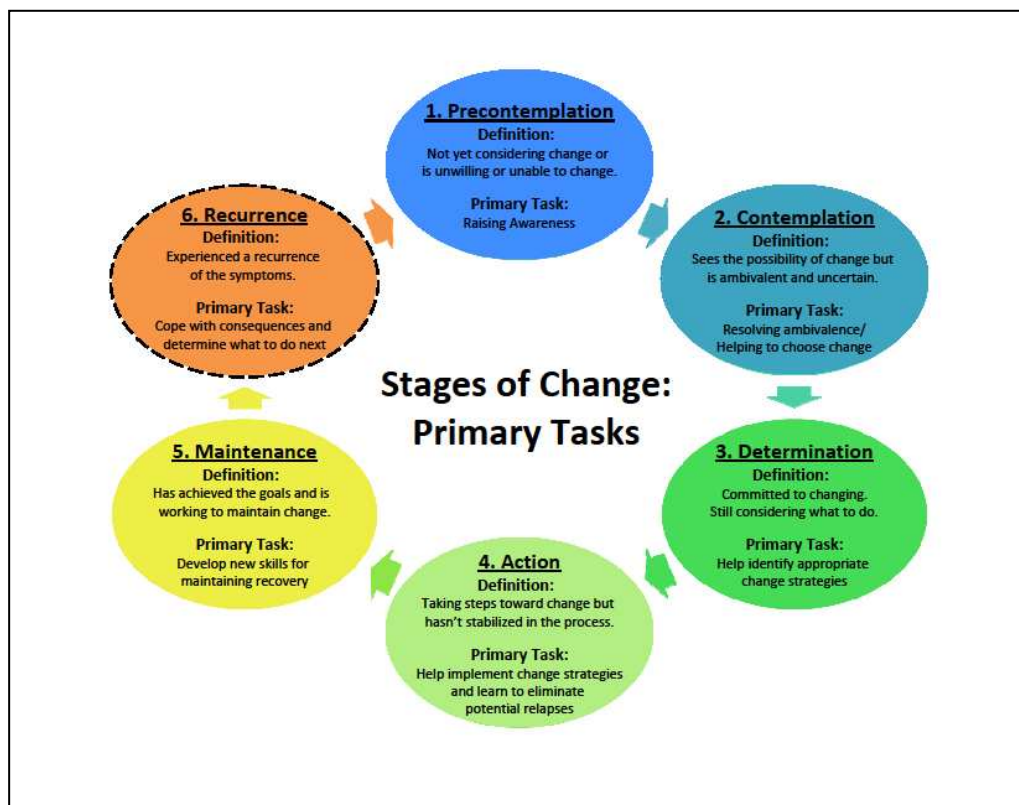


Figure 1-7 The trans-theoretical model of change by Prochaska and DiClemente

Despite the variation in intensity and duration, at their core, very brief or intense modalities of interventions aim to motivate change and promote awareness of the harmful effects of drinking. While in the alcohol literature, “brief advice” may sometimes be used to differentiate more simple interventions from multiple extended

sessions of counselling, for clarity, the term “alcohol brief intervention” is used flexibly to refer to the entire family of brief interventions in this thesis.

1.7.2.3 Supportive evidence for the effectiveness of brief interventions

There is more evidence in support for screening and brief interventions than there is for any other treatment for alcohol problems(115,125–128). Across over 56 trials and at least 13 systematic reviews/meta-analyses conducted internationally and across several healthcare settings, the general preponderance suggest that alcohol brief interventions can reduce hazardous or harmful alcohol consumption.

1.7.2.4 Brief interventions in primary healthcare

Weekly alcohol consumption is the most frequently reported outcome in most trials of brief interventions. A meta-analysis involving over 22 RCT’s and 5800 patients found that brief interventions reduced the amount of alcohol consumed among men and women by 38 grams per week, which approximates to almost a 5 unit reduction, using the current UK unit conversion (Mean difference: -38 grams per week, 95% CI: -54 to -23)(128). This review included efficacy trials i.e. trials carried out in more naturalistic conditions of primary care, and is therefore more relevant to real routine practice than most other reviews.

Another more recent systematic review assessing the effectiveness of brief interventions delivered in primary care found higher effect sizes. Brief interventions reduced alcohol consumption by 49g per week among adolescents and adults in primary care(129). Restricting the analysis to only older adults (adults over 65years) however showed a lower effect size which was more comparable to that of Kaner et al(128).

There have been some indications from previous data that women are less likely to respond to brief interventions than men. For example, subgroup analyses by sex in the review by Kaner et al found huge differences in effect of brief interventions between men (mean difference = -57 g, 95%CI: -89 to -25 g week) and women (mean difference = -10 g, 95%CI: -48 to 29 g week)(128). The relatively small sample of women (n=499) included in this analysis may partly explain the lower effect. Indeed, in another systematic review where data on over 1000 women was used, Ballesteros and colleagues found no difference in the effect size of brief interventions between men and women(130). Two other reviews have also found that brief interventions have equal effectiveness in men and women(126,131).

Overall, the effect size of brief interventions is more understandable in terms of number needed to treat (NNT – the number of hazardous or harmful drinkers that need to receive intervention for one to reduce drinking to low risk levels). On average, it is estimated that for every 8 to 10 people who receive an alcohol brief intervention in primary care, one will go on to reduce their alcohol consumption to safe levels. There have been arguments that NNT may underestimate the full effectiveness of brief intervention since, even if the drinker does not immediately reduce drinking, it may “plant a seed” that later becomes an active effort to cut down. Irrespective of this concern, the NNT for brief alcohol interventions compares favourably with the NNT for smoking cessation advice which has been estimated to be about 20(132).

1.7.2.5 Brief interventions in secondary care

A larger reduction in alcohol consumption has been shown in secondary care patients who receive brief interventions. The 2011 Cochrane review by McQueen et al found these effects across different periods of follow-up. At follow-up of 6 months,

individuals receiving brief interventions reduced their consumption by 69g [Mean difference (MD) in consumption -69.43 (95% CI -128.14 to -10.72)] (133). At 9 months, a far greater reduction of 182g was found comparing those with brief interventions to the control group. [MD -182.88 (95% CI -360.00 to -5.76)] Although studies in primary and secondary care are not directly comparable given the difference in settings, these higher effects seen in secondary care may be due to the fact that, in some ways, hospital settings offer a more conducive environment for brief interventions mainly because patients have more time available(133).

1.7.2.6 Other effects of brief interventions

In both primary and secondary care studies of brief interventions, other outcomes such as injuries, healthcare use and mortality have been reported. A trial by Gentilello and colleagues found that brief interventions delivered in secondary care led to a 48% reduction in rates of injuries at three-year follow up(134). Another trial found that there were 0.5 fewer Emergency department visits in people randomly assigned to receive brief interventions compared to a control population(135).

1.7.2.7 National recommendation for brief interventions

There are strong recommendations for the use of screening and brief interventions in the UK as reflected in several alcohol policy documents with the Royal College of Physicians report in 2001 being one (95). Other relevant documents include the 2004 'Alcohol harm reduction strategy', the 2008 'Reducing Alcohol Harm: health services in England for alcohol misuse' document and most recently the 2013 'Health First: an evidence-based alcohol strategy for the UK' document (5,93,136).

Currently, several national systems of financial incentives which encourage delivery of brief interventions in primary care exist, but these are restricted to only specific groups of patients and there is still the need for more comprehensive national and local responses to improve implementation. For example, the **Alcohol direct enhanced services** guidance introduced in 2008, recommends and rewards practices for the screening of newly registered patients (137). The **Quality and Outcomes framework** has an indicator for alcohol screening, but this only rewards screening activity in mental health patients (138). There is also the **NHS health check** alcohol screen which is paid for as a commissioned service, this however covers only patients who are between 40 – 75 years and is expected to be done every 5 years(139).

1.7.3 Acceptability and implementation of screening and brief interventions

Recommendations for the use of brief interventions is now wide spread. Several studies in the UK have found that brief alcohol intervention have high levels of acceptability to patients and some care providers but within particular contexts. These include the first time a patient registers with a practice, when they are being managed for a chronic disease or when alcohol screening and intervention is integrated with screening for other lifestyle behaviours(140).

There are currently no longitudinal studies exploring the implementation of screening and brief alcohol interventions in the UK despite the strong recommendations and acceptability. However, in 2003, it was reported that GPs in England identified only 2.1% of patients with alcohol-use disorders(141). A more recent cross sectional study which evaluated screening of newly registered patients in primary care using the THIN database, found 76% of new patients had been asked about their drinking habit,

however it was reported that screening was done using a validated screening tool in only 9% of all records(142).

In common with any intervention programme there are bound to be barriers which may affect implementation and several barriers to alcohol care in the UK have been documented(143–145). Within primary care where there are several competing priorities, lack of time is often cited as an important barrier to provide alcohol care. There is also the issue of role insecurity whereby some healthcare staff feel insufficiently qualified to provide advice on alcohol. Lack of or poor financial reimbursement is also often cited as an important disincentive(146). Until recently, there have been no reimbursements attached to the provision of brief alcohol interventions although delivery of some other similar behavioural interventions like smoking cessation is reimbursed. Other barriers that have been used to justify low implementation include a lack of organisational support and resources for implementation e.g. lack of screening questionnaires and lack of specialist services for onward referral; scepticism about the benefits of the brief interventions; and finally, perceived potential of provoking negative reactions among patients(115,147,148).

Besides these organisational and attitudinal barriers, there are some other patient level factors that may interact with practitioner's attitudes to potentially influence the provision of brief intervention. For e.g. data suggests that practitioners are more likely to approach men about their drinking than women(145,148,149). Whilst these may be an attitudinal factor arising from the fact that heavy drinking is more likely to be prevalent among men, it could also be that practitioners attitudes have been shaped over time by recognition that fear of stigmatisation may make women less responsive to conversations about alcohol use.

With respect to age, in an interview of 24 Danish general practitioners Beich et al found that most practitioners questioned the rationale for screening young populations as they felt this population would outgrow harmful drinking patterns. The implication of this was that practitioners were less likely to deliver interventions to younger age groups(150). By contrast, Lock et al found age did not independently predict a brief intervention in their assessment of 926 patients in England who had been screened and offered interventions. The difference in study setting and the fact that intervention in the study by Lock et al was delivered by nurses may account for the difference in attitude towards age(151).

Clearly, there are a number of complex barriers to the intervening for alcohol use. The effectiveness of brief interventions could be strengthened if solutions are found to some, if not all of these barriers. Some potential solutions which have been provided by on-going research are discussed within the studies conducted in this thesis.

1.7.4 Other interventions for alcohol misuse that can be offered following screening

1.7.4.1 Referral to specialist

With evidence that brief interventions may not be very effective for people with severe alcohol problems, NICE recommends onward referral to specialist treatment centres of patients found to be drinking at levels of dependence, patients with obvious alcohol related physical complications e.g. liver disease or patients who are unresponsive to brief extended advice (117).

1.7.4.1.1 Pharmacotherapy

NICE also recommends prescribing of pharmacological interventions to patients who are found to be dependent. There are three pharmacological medications currently recommended for use in England, Naltrexone, Acamprosate and Disulfiram. However, prescribing reports suggest that only Acamprosate and Disulfiram are currently prescribed and these prescriptions have been for only a minority of NHS users(136).

1.8 Summary and Justification of thesis

Overall, it has been demonstrated that alcohol related problems especially alcoholic cirrhosis and mental and behavioural disorders have increased remarkably in the UK. Thus far, the preponderance of evidence suggests that alcohol brief interventions are acceptable and can be effective in motivating people to reduce their alcohol consumption to safer levels where there is less risk of developing alcohol related complications. NICE guidelines endorsed by several Royal Colleges, recommend that this strategy should be integrated to routine clinical practice. However to date, little is known about the extent of implementation of this strategy in medical practice in the UK and there have been no longitudinal studies exploring this.

Additionally, as most of the evidence on brief intervention effectiveness is obtained from controlled environments, it is unclear whether there are opportunities in clinical practice for practitioners to identify those most at risk of developing alcohol-related disease and deliver brief interventions. Information on healthcare utilisation, comorbidities and any other clinical characteristics associated with people who later develop alcohol disorders may better highlight the opportunities for earlier identification and prevention of such disorders, but as described earlier, these are generally lacking.

By investigating prior consulting patterns of individuals with alcoholic cirrhosis and psychosis, this thesis will provide the much needed evidence on whether there are early signs (e.g. more frequent healthcare use for specific conditions) that identify this at-risk group for interventions. By assessing the recording of brief interventions in patients prior to when alcohol use disorders are diagnosed, the extent of

implementation in clinical practice would also be highlighted to fill an apparent knowledge gap.

1.9 Thesis aims and objectives

The overall objectives of the thesis are therefore as follows:

1. To estimate patterns of healthcare utilisation in patients during the period before alcoholic cirrhosis is diagnosed in comparison to individuals in the general population of similar age and general practice, and assess whether there are differences between men and women.
2. To estimate the extent to which alcohol use and alcohol brief interventions were documented for individuals prior to the diagnosis of alcoholic cirrhosis in comparison to individuals in the general population of similar age and general practice, and assess whether there are differences between men and women.
3. To estimate patterns of healthcare utilisation in patients during the period before alcoholic psychosis is diagnosed in comparison to individuals in the general population of similar age and general practice, and assess whether there are differences between men and women.
4. To estimate the extent to which alcohol use and brief alcohol interventions were documented for individuals prior to the diagnosis of alcoholic psychosis in comparison to individuals in the general population of similar age and general practice, and assess whether there are differences between men and women.

1.9.1 Outline of thesis chapters

The subsequent chapters of the thesis describe the management of the thesis data and four separate studies that address the thesis objectives. The outline below gives a brief description of the content of each chapter:

Chapter 2 describes the Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics database, the two datasets used for all the studies in the thesis. The methods used in identifying the study populations as well as information on how study outcomes were defined are provided in **Chapter 3**. **Chapter 4** reports the first study which investigates the patterns of primary and secondary care utilisation, alcohol misuse screening and alcohol interventions in patients prior to the diagnosis of alcoholic cirrhosis, stratified by gender. Following this study, alcohol-attributable healthcare attendances in patients with alcoholic cirrhosis are investigated using a case-control design, and the results of this study are reported in **chapter 5**.

The study presented in **Chapter 6** examined prior patterns of healthcare utilisation, alcohol misuse screening and alcohol interventions in patients with alcoholic psychosis, in a similar way as chapter 4. This is again followed by another case control study (**Chapter 7**) which investigates alcohol-attributable healthcare attendances in patients before psychoses diagnosis. In **Chapter 8**, a summary of the entire thesis is provided including a reflection on its strengths, limitations and recommendations for future research.

Chapter 2

2 Description of study data

This section describes the datasets used for the studies within this thesis.

2.1 Introduction to Clinical Practice Research Datalink (CPRD)

Primary care data for this thesis was obtained from the Clinical practice Research Database (CPRD). The CPRD (152) is a primary healthcare database containing anonymised medical, prescription, lifestyle and socio-demographic information of individual patients from General practitioner practices across the UK (England, Wales, Scotland and Northern Ireland) (153,154). It was set up in 1987, initially as a commercial venture by Reuters Health information, but was donated to the Department of health in 1994 and is now widely used for epidemiological research (155–158). The Medicines and Health Research Agency (MHRA), UK's regulator of medicines and devices currently manages and administers the CPRD database. In 2012, when the data for this thesis were first extracted, CPRD included data of 12million patients from 660 UK general practices; 5.5 million of these patients are alive, actively registered and can be followed prospectively while the remaining patients have historical data but have either died or left the practice.

General practices in the UK that contribute to the CPRD enter their data into the database prospectively using the Vision Software which enables the data to be subsequently used for research purposes. Data recording typically occurs during patient consultations; however, practices may retrospectively enter a patient's consultation/events from a period prior to their registration with that practice if it is considered significant. The data recorded within the CPRD includes patient demographics such as year of birth and gender; some lifestyle characteristics such as

smoking behaviour and drinking status; medical diagnoses; prescriptions issued by GPs, referrals to specialists, laboratory test results, and correspondences received from secondary care e.g. discharge summaries.

2.1.1 Data Validity

The MHRA conducts an audit on the raw data entered by each CPRD practice to check for completeness, continuity and credibility in specific areas. This audit is usually done at both the practice level and patient level. At the practice level areas such as rates of consultations, referrals or the number of prescriptions per patient are checked and successful practices are assigned an “up to standard” date, defined as the date from which their data are considered suitable for inclusion in research based on these audit parameters. At the individual level, consistency in patient details such as age, sex and registration details are checked and patients found to have internally consistent records are labelled within the dataset as “acceptable” for inclusion in CPRD (159).

2.1.2 Data coding

Within the database, clinical data are recorded using the Read coding system, a hierarchical coding system based on the International Classification of Diseases (160,161). During or after a patient consultation at a practice, the GP enters a descriptive term for the patients presenting symptoms or diagnosis and chooses the most appropriate Read code from a drop down list of possible Codes (159). The use of this standard clinical coding system is widespread across General practices in the UK and Read codes are currently managed by the UK Terminology Centre.

2.1.3 Data format of the CPRD

At the time of data extraction for the work contained in thesis (2012) the CPRD data were organised into 9 separate files. The nine files comprised a clinical data file, a consultation data file, a patient data file, a practice data file, an immunisation data file, a referral data file, a therapy data file, a test data file and an additional data file. Patient records across all files can be linked using a unique patient identifier which is composed of an encrypted practice identification number and an encrypted patient identification number. Table 2-1 below gives a summarised description of the main files that were used in this thesis.

Table 2-1 File structure of the data files in CPRD

CPRD File name	Content
Clinical data file	Contains information recorded each time a patient has a clinical event and includes Read coded diagnosis or symptom, the event date, outcome of consultation e.g. referral, clinical specialty providing consultation, and location of consultation
Consultation data file	Contains information recorded each time a patient has a consultation, and includes consultation date, the consultation type e.g. face-to-face or telephone encounter, location of the consultation and the specialty providing the consultation
Patient data file	Contains personal details of a patient including patient's year of birth, registration date with a practice, "acceptable" status, and if applicable date of transfer out of a practice, transfer out reason and date of death.
Referral data file	Contains information recorded each time a patient is referred externally for care.
Therapy data file	Contains information on prescriptions issues to a patient and includes information such as the prescription date, prescription duration, prescription quantity, and the dosage value
Additional data file	Contains data recorded on other aspects of clinical care, for example, data on test results, patient weight, smoking status and alcohol intake.
Practice file	Contains practice level information such as practice location, the practice "up to standard" date, and the last collection date (the last date of data collection from the practice)

2.2 Hospital Episode Statistics (HES) data

Data on hospital admissions used for this thesis were obtained from the HES database. The HES database contains records of all admissions within NHS hospitals in England from 1989 onwards (162). It is the largest national admissions database worldwide and more than 12 million new records are added to the database each year. The available data within HES includes information on patient demographics such as sex, date of birth and region of residence; admission diagnosis coded using the International Classification of Diseases 10th revision (ICD 10); as well as administrative details such as admission and discharge dates. Each admission record of a patient within HES consists of a number of records called “episodes”. An episode represents the time period a patient was under the care of a particular consultant during an inpatient admission. As a patient may be transferred from one consultant to another during their admission, an admission can have more than one episode. Each episode can have up to 20 diagnoses which comprise one primary diagnosis and up to 19 secondary diagnoses and then up to 24 procedures coded using the United Kingdom Tabular List of the Classification of Surgical Operations and Procedures (version OPCS4). For the purpose of this research, all recorded diagnoses for each admission were assessed regardless of whether it was a primary or secondary diagnosis.

2.2.1 Data format

At the time the studies within this thesis were conducted (2012), HES data were structured in 9 files namely a patient data file, a hospitalisation data file, an episodes data file, a diagnoses data file, a procedures data, a critical care data file, an

augmented care periods data file, a maternity data file, and a source date file. Table 2-2 summarises the description of the HES files used for this thesis.

Table 2-2 File structure of the data file contained in HES

CPRD File name	Content
Patient file	Contains information on patient demography including year of birth, sex and ethnicity
Hospitalisation data file	Contains information recorded each time a patient has a hospitalisation and includes the date of admission and discharge, the method of admission and for each admission, a unique admission identification number.
Episodes data file	Contains episode level information for each admission and in addition to admission and discharge dates contains date for each episode, and a unique number which identifies the admission to which each episode belongs to.
Diagnoses data file	Contains information on all primary and secondary diagnosis a patient has had while on admission including the date the diagnosis was made, and the episode the diagnosis is attached to. As aforementioned, patients may have up to 20 admissions per diagnosis.

2.3 Data Linkage

Data in CPRD and HES have been linkable from 1997 onwards. This linkage was done by a third party using a combination of a patient's sex, date of birth, postcode and NHS number (163–165). Over 90% of patients had their records matched exactly using their NHS number, with the remaining patients linked probabilistically on the basis of the other three variables-sexes, data of birth and post-code. Before this data linkage was done, participating CPRD practices had to give their consent. At the time the first two studies of this thesis were conducted, 365 English practices (50% of all CPRD practices) had given consent hence only patients within these practices could therefore be linked. At the time of the last two studies, the number of linkable English practices had increased to 398. This thesis made use of only data from linked CPRD GP practices in order to gain comprehensive understanding of patient's use of health care services through both primary and secondary care. The linkage was available for the period between April 1st 1997 and 31st March 2012 for the version of data used for the first two studies, and between April 1st 1997 and 31st April 2014 for the version of data used for the latter two studies.

2.4 Justification of using CPRD

The CPRD and linked HES data are widely used valuable data sources for epidemiological studies. However like all data sources there are some inherent limitations which should be borne in mind. The following section discusses some of the advantages and potential imitations of linked CPRD and HES with respect to the studies conducted within this thesis.

2.4.1 Relevant data

CPRD has information on alcohol consumption status, alcohol brief interventions and alcohol related referral recorded prospectively within the dataset. In addition to this alcohol information, it also contains information on healthcare utilisation which is recorded prospectively and is therefore useful to comprehensively study prior patterns of healthcare use of individuals. One thing to note however is that these data invariably lack information on non-attenders of GP services which needs to be borne in mind when interpreting the results of studies using routinely collected healthcare data.

2.4.2 Size

The large size of the CPRD and HES database makes it particularly suitable to study relatively rare diseases (166,167) including alcoholic cirrhosis and alcoholic psychosis, with sufficient statistical power. In addition to the power, this large size will also give more precision to estimates of healthcare utilisation than can be afforded from smaller clinical studies.

2.4.3 Representativeness

Although the GP practices contributing data in CPRD are self-selected, CPRD patients are broadly representative of the entire UK population in terms of age and sex distribution (168,169). This combined with the national coverage of HES, makes it plausible to assume that findings using CPRD and HES can be generalised to the UK population as a whole. One potential limitation to this generalisability in this thesis however is that only data from linked CPRD practices which represent just above 50% of all CPRD English practices are used. However, this is unlikely to significantly affect representativeness as a recent study has shown that non-linked GP practices are not systematically different from linked practices (169).

2.4.4 Prospectively collected data

As mentioned previously, the majority of medical conditions and symptoms within the CPRD are prospectively entered into the database as part of the general course of medical care for each patient. As a large part of this thesis focuses on retrospective analysis of patient's previous medical encounters with primary and secondary care, this method of data collection is of an added advantage. It provides good insight to the medical history of patients, while greatly minimising potential recall bias that would have been unavoidable using cross-sectional clinical based studies.

2.4.5 Data validity

The MHRA maintains strict standards of the CPRD data. This is done through practice level and patient level data checks already described in section 2.1. Additionally, there is also the opportunity for the data to be independently validated by third parties, although as this comes with a high cost it prohibits the validation of a large number of patient data. The third party validation is usually done through a process which

involves examining samples of paper records to check for consistency with electronic records or by asking GPs of relevant practices to fill out a questionnaire to validate particular information of interest within the database. Using this process, CPRD has been extensively validated for a wide range of diagnoses including liver disease and has been found to have a high mean positive predictive value of 89% (159). HES however cannot be externally validated by researchers because the computerised records are completely anonymised. However a recent NHS audit found 91% accuracy in diagnostic coding within HES (170).

2.4.6 Incomplete recording

As with any routinely available datasets, there is the concern that what is recorded in CPRD is not necessarily determined by the needs of research. This means that recording could be purely driven by what GPs and other health professionals deem to be important to the care of a patient. This issue is particularly relevant to the recording of alcohol information. So for example, practitioners may be unlikely to record that alcohol use screening was conducted in a patient unless the patient suffered from a condition that could potentially be attributable to alcohol. Likewise, there is the likelihood that results indicating heavy drinking may be more likely to be recorded as this may affect a patient's health. To an extent, in recent years, this limitation may have been addressed with the introduction of the Quality and Outcomes framework, an incentive contract for all GP practices in the UK. The QOF rewards GPs based on how well they provide care for patients and practices receive score points based on the completeness of records of certain clinical indicators (138). There are indicators which reward the recording of a wide range of diagnosis as well as preventive activity including smoking status and smoking cessation activity. However for alcohol specifically, although there is a QOF indicator, it is limited to recording of

alcohol related activity in specific population groups e.g. patients with mental health problems. The implication of this is that in certain cases, not only will alcohol consumption or intervention data be incomplete but there may be a systematic bias as to which data are missing.

2.4.7 Gaps in alcohol consumption data

In addition to the issue of incomplete recording, as with other routine databases, alcohol data in CPRD is self-reported. It is widely believed that people tend to underestimate their drinking levels (39,171); therefore it is reasonable to assume that these data will consequently represent an extent of inaccurate reporting.

In addition, there are more than 280 Read codes available to GPs to record alcohol related information. These include some non-specific codes which do not specify frequency or volume of consumption for example, codes for “beer drinker”, “spirit drinker” or “wine drinker”. Such coded data are not sensitive for differentiating between levels of drinking (i.e. whether a person is a low risk or high risk drinker) and therefore by using these data, there is the increased potential for misclassification of patients drinking status. However, given that most patients in CPRD with an alcohol related Read code also have information on absolute volume of consumption in units, the effect of this potential coding bias is unlikely to be large.

2.4.8 Duration of follow up

Despite the seemingly large size of the CPRD database, people do not contribute data over the entire duration of the database. The average observation time for people with alcoholic cirrhosis and psychosis in this thesis was 5 years, although few patients had a maximum observation period of 15 years. In practice, this leaves little time being

available to assess pre-diagnosis exposures in some patients, although it surpasses other data where cross-sectional designs are used.

2.5 Summary of data strengths and limitations

Overall despite some limitations, using the HES dataset in combination with the CPRD would appear to offer the best source of data to gain a comprehensive and generalisable understanding of patient journeys through primary and secondary care before the diagnosis of the diseases to be studied in this thesis, without the costs involved in primary data collection and its associated potential for recall bias.

2.6 Ethical approval, anonymity and data management

Ethical approval for the use of the datasets was obtained from the Independent Scientific Advisory Committee (ISAC) for the MHRA database research (approval reference numbers 14_194R and 15_073R).

In April 2012 and subsequently in January 2015, the CPRD and HES data were obtained under the University of Nottingham License in anonymised form in the form of flat files. I subsequently conducted all data management, cleaning, data extraction and analysis using the v12.0 of the Statistical software Stata (StataCorp, Texas).

Chapter 3

3 Building the thesis datasets

This chapter describes how the study populations were defined for the studies conducted in this thesis. The methods used in defining healthcare encounters, alcohol related outcomes and potential confounding variables are also described in this chapter.

3.1 Definition of the alcoholic cirrhosis population

3.1.1 Patient selection

To conduct the studies on alcoholic cirrhosis, two population datasets needed to be built. The first was a population of incident cases of alcoholic cirrhosis diagnosed during the period for which linked data were available. At the time of this study, the linked data were available for the period between April 1997 and March 2012. The second was a population of patients without alcoholic cirrhosis who would serve as a control group.

To create the first population, all CPRD patients eligible for linkage with a recorded diagnosis of alcoholic cirrhosis in either primary or secondary care were identified using the codes listed in Table 3-1. These codes were adapted and updated from previous validated definitions by Ratib et al (172). Though there are other cirrhosis codes for which the underlying aetiology is alcohol, only these precise codes were used in this study to increase the specificity of alcoholic cirrhosis diagnosis.

Table 3-1 Read and ICD-10 codes for Alcoholic cirrhosis

Code	Term
Read	
J612.00	Alcoholic cirrhosis of liver
G852300	Oesophageal varices in alcoholic cirrhosis of the liver
J612000	Alcoholic fibrosis and sclerosis of liver
ICD-10	
K70.3	Alcoholic cirrhosis of liver
K70.2	Alcoholic fibrosis and sclerosis of liver

3.1.2 Date of diagnosis

Each patient with alcoholic cirrhosis was assigned a date of diagnosis defined as the date of the first record of any alcoholic cirrhosis code in either primary or secondary care as listed in Table 3-1.

3.1.3 Inclusion and exclusion criteria

All patients whose diagnosis date occurred before the primary care practice ‘up to standard’ date, 1st April 1997 (date from which CPRD and HES can be linked), or within 1 year following registration with a general practitioner were excluded. The purpose of exclusion using the 1 year post registration threshold was to ensure that only incident rather than prevalent cases were included in the study. As demonstrated by Lewis et al (173), since in CPRD retrospective diagnoses are sometimes entered into patient records at the time they newly register with a practice or when the practice first joins CPRD, including patients with a diagnosis recorded within 12 months after the date of registration is likely to result in a misclassification of prevalent cases as incident.

Patients whose diagnosis was recorded after the date that the patient transferred out of practice, date of death or the date of last data collection for the practice were also excluded as in such cases it was no longer possible to ascertain the exact date of diagnosis. Further exclusions were patients whose records were deemed “unacceptable” by the MHRA, patients with invalid diagnosis date codes and patients who were less than 18 years old at date of diagnosis.

3.1.4 Selection of control population

Selecting a control population with similar characteristics to cases is an efficient way of ensuring that any differences identified between cases and controls are as a result of

the disease status rather than other characteristics. Moreover it is also the best way to control for certain characteristics or confounders (e.g. general practice) that cannot be adjusted for in the analysis due to too many strata. Bearing this in mind, age and GP practice have been shown to be strong confounders/determinants of healthcare utilisation. Therefore the objective here was to select a control population that comprised of patients who were of a similar age and from the same GP practice as the identified cases. To make optimal use of the large size of the CPRD database, a ratio of 10 controls to 1 case was chosen.

Controls were identified using linked General practices as was the case for the selection of cases. Eligible controls were all adult patients without a diagnosis of alcoholic cirrhosis or a diagnosis of any condition for which the differential diagnosis could have been alcoholic cirrhosis (i.e. unspecified cirrhosis or oesophageal varices). For each case, the 10 controls selected were selected randomly but matched on general practice and ± 5 years the age of the case. The matching process used was frequency matching(174) rather than individual matching which ensured that the frequency distribution of age and General practices within the control population was similar to that of the case population. By employing this matching design i.e. frequency matching instead of individual matching, the opportunity to assess for interactions between age and the thesis outcomes was retained.

Each selected control was then assigned a pseudo-diagnosis date, which was a randomly generated date between 1 year after the start of the linked dataset (1997) and the date the patient left the practice or died.

3.2 Defining the alcoholic psychosis study population

A similar methodology as described above was used in defining the population of patients with an incident diagnosis of alcoholic psychosis. However, as there have been no previous validations of the codes used in CPRD/HES for alcoholic psychosis, additional analyses that evaluated the validity of the codes used in this thesis and the identified population were conducted and are described in full detail below.

3.2.1 Datasets

Both primary and secondary care data (described in detail in chapter 2) were used to identify cases of alcoholic psychosis for the validation. Data used were from all 398 CPRD GP practices that have consented for linkage to HES at the time the studies on alcoholic psychosis were conducted. For this study, the linkage to HES was for the period between April 1st 1997 and June 30th 2014.

3.2.2 Patient selection

3.2.2.1 Case definition

Alcoholic psychosis was initially defined in two ways and both definitions were assessed with regard to how they altered the study population.

Definition 1: this broad definition selected all possible cases of alcoholic psychosis using Read and ICD 10 codes that specified alcoholic psychosis as well as codes for alternative descriptions of the disease including “alcoholic paranoia”, “alcoholic hallucinosis” and “alcoholic dementia”.

Definition 2: This definition was more restrictive and included only patients identified with alcoholic psychosis diagnostic codes that made specific mention of the terms “alcohol” and “psychosis”. The full list of codes used for both definitions are provided in Table 3-2.

Table 3-2 Read and ICD-10 codes for alcoholic psychosis based on the broad and restrictive definitions.

Code	Broad definition	Restrictive definition
Codes and description		
Read codes		
Eu10513	[X]Alcoholic paranoia	
E011000	Korsakov's alcoholic psychosis	
E015.00	Alcoholic paranoia	
Eu10514	[X]Alcoholic psychosis NOS	[X]Alcoholic psychosis NOS
E011100	Korsakov's alcoholic psychosis with peripheral neuritis	
E01z.00	Alcoholic psychosis NOS	Alcoholic psychosis NOS
Eu10711	[X]Alcoholic dementia NOS	
E01y.00	Other alcoholic psychosis	Other alcoholic psychosis
Eu10511	[X]Alcoholic hallucinosis	
E01..00	Alcoholic psychoses	Alcoholic psychoses
E01yz00	Other alcoholic psychosis NOS	Other alcoholic psychosis NOS
1B1c.00	Alcohol induced hallucinations	
Eu10500	[X]Mental & behaviour dis due to use alcohol: psychotic disorder	
E011200	Wernicke-Korsakov syndrome	
Eu10611	[X]Korsakov's psychosis, alcohol induced	
ICD10 codes		
F10.5	Mental & behavioural disorder due to use of alcohol: psychotic disorder	Mental & behavioural disorder due to use of alcohol: psychotic disorder
F10.7	Mental & behavioural disorder due use alcohol : residual & late-onset psychotic disorder	Mental & behavioural disorder due use alcohol : residual & late-onset psychotic disorder
F10.8	Mental & behavioural disorder due to use of alcohol: other mental & behavioural disorder	
F10.9	Mental & behavioural disorder due use alcohol: unspecified mental & behavioural disorder	

3.2.3 Date of diagnosis

For each identified patient, the date of the earliest recorded code for alcoholic psychosis in either primary or secondary care was chosen to represent the diagnosis date of alcoholic psychosis.

3.2.4 Inclusion and exclusion criteria

Similar to the criteria used for the alcoholic cirrhosis population, all patients diagnosed before the primary care practice 'up to standard' date, 1st April 1997 (date from which CPRD and HES can be linked), or within 1 year following registration with a general practitioner were excluded. Patients whose diagnosis was recorded after the date that the patient transferred out of practice, date of death or the date of last data collection for the practice were also excluded. Further exclusions were patients whose records were deemed "unacceptable" by the MHRA, patients with invalid diagnosis date codes and patients who were less than 18 years old at date of diagnosis.

3.2.5 Control selection

Again, similar to the control selection process for alcoholic cirrhosis, a total of 10 controls frequency matched by age (± 5 years) and GP practice were selected for each case. Controls had to be without any record of any psychosis prior to their pseudo-diagnosis date; this allowed the exclusion of patients with psychosis that may be alcohol related but is not recorded as such from the comparison population.

3.3 Identifying evidence to substantiate the codes used for selecting the alcoholic psychosis population.

To evaluate the validity of the alcoholic psychosis diagnosis in identified cases several steps were taken for cases identified using each definition.

3.3.1 Patient grouping

First, cases were divided into three groups based on where their psychosis diagnosis was recorded as follows:

Group A: patients who had a recorded diagnosis in CPRD and no recorded diagnosis in HES

Group B: patients who had a recorded diagnosis in only HES and no diagnosis throughout CPRD

Group C: patients who had a diagnosis in both HES and CPRD.

3.3.2 Identifying supporting evidence

For patients in group A, an assessment of their hospital records was conducted to identify whether there were any corresponding legitimate codes in the linked hospital admission data which could substantiate their diagnosis. Codes used to assess patient's hospital records included codes that specifically or non-specifically indicated a mental or behavioural disorder. Full code list is available in Appendix 1.

For patients in group B, all primary care records were assessed in order to identify if there was any primary care record broadly relating to the hospital admission for psychosis which could substantiate the diagnosis. (Full code list is available in Appendix 2).

For both groups of patients, all therapy records 60 days before and after the diagnosis of alcoholic psychosis were assessed to identify prescriptions for anti-psychotic or mood stabilising drugs including thiamine, antidepressants, hypnotics and anxiolytics.

Full code lists used in identifying relevant medications are in Appendix 3.

For patients in group C, who had a diagnosis of alcoholic psychosis in both CPRD and HES, this was considered sufficient to categorise as patients with alcoholic psychosis and so no further validation was explored.

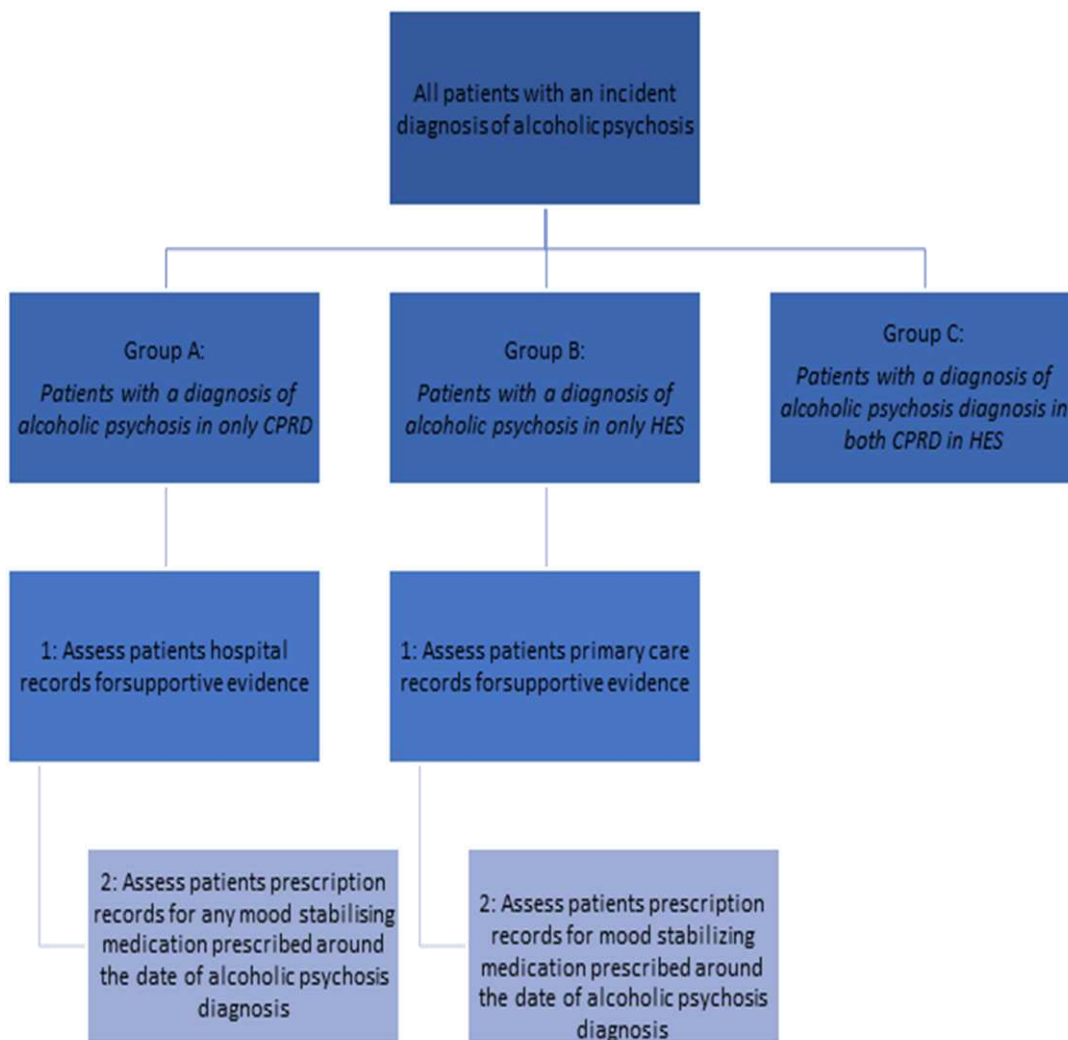


Figure 3-1 Summary of the process used in identifying evidence to substantiate the diagnosis of alcoholic psychosis

3.3.3 Results

The proportion of patients identified using each definition is shown in Table 3-3 and Table 3-4.

A total of 1,731 cases of alcoholic psychosis were identified using the broad definition while a subset of 878 patients was identified with the less inclusive definition.

Compared to the broad group, the less inclusive group were of a slightly older age, but had similar observation time and distribution of men and women. In terms of location of diagnosis recording, a broadly similar proportion in each group had their diagnosis recorded in only primary or only secondary care.

Table 3-3 Description of the population of alcoholic psychosis identified using two case definitions

	Definition 1 (broad) n=1,731	Definition 2 (restricted) n=878
Age at diagnosis (years)		
Mean (SD)	53.3(17.4)	55(16.2)
Age group (n, %)		
18-44	595(34.4)	245(27.9)
45-54	334(19.3)	179(20.4)
55-64	335(19.4)	198(22.5)
65-74	236(13.6)	141(16.6)
≥ 75	231(13.3)	115(13.1)
Observation time (years)		
Median(IQR)	5.5(2.6-9.2)	5.2(2.5-9.0)
Sex (n, %)		
Male	1,156(66.8)	607(69.1)
Female	575(33.2)	271(30.9)

Table 3-4 **Number of cases identified by each definition, stratified into the three patient groups.**

	Definition 1	Definition 2
	n (%)	n (%)
GROUP A	464(27.0)	263(30.0)
GROUP B	1,109(64.0)	548(62.4)
GROUP C	158(9.2)	67(7.6)
Total number of patients in cohort:	1,731	878

GROUP A: patients whose diagnosis are recorded in only CPRD

GROUP B: Patients whose diagnosis are recorded in only HES

GROUP C: Patients with a diagnosis recorded in both CPRD and HES

3.3.3.1 Supporting evidence - definition 1

3.3.3.1.1 Group A

Of the 464 patients with a diagnosis of alcoholic psychosis in CPRD alone, n=399 (86.0%) had at least one hospital admission broadly relating to psychosis while n=329 (71%) had a prescription for at least one antipsychotic or general mood stabilising drug. Combining these results, a total of 438 patients (94.3%) out of the 464 identified in CPRD alone had a hospital admission, an antipsychotic therapy or both to complement their diagnosis.

3.3.3.1.2 Group B

Of the 1,109 patients with a diagnosis in only HES, 800 patients (72.1%) had a primary care record broadly relating to psychosis while 658 (59.3%) had prescriptions for antipsychotic or other mood stabilising therapy. Of those with primary care records, n=580 had codes that specifically indicated mental health problems while n= 220 had at least one generic record around the diagnosis of alcoholic psychosis which was likely to be linked to the hospital admission for psychosis. Examples of such generic codes include codes for “discharge summary” “discharged from hospital” or “seen in hospital casualty”. Combining all results, a total of 943 patients (85.0%) out of the 1,109 patients identified as having a diagnosis in only secondary care had additional evidence in their primary care records to confirm the diagnosis.

3.3.3.1.3 Group C

By definition, 100% of the 158 patients in this group have supportive evidence.

3.3.3.1.4 Summary of validation of cohort identified using definition

1

In summary, 94.3% of those identified in primary care had supportive evidence in HES, while 85% of those identified in secondary care alone had supportive evidence in primary care. Combining these results, of all 1,731 patients with a diagnosis of alcoholic psychosis identified using the broad definition, 89% had supportive evidence to complement their diagnosis (Table 3-5).

Table 3-5 Cases of alcoholic psychosis with supporting evidence

Alcoholic psychosis diagnosis	n	Numbers(%) with supportive evidence
CPRD only (Group A)	464	438(94.3%)
HES only (Group B)	1,109	943(85.0%)
CPRD & HES (Group C)	158	158 (100%)
TOTAL	1,731	1,539(89%)

3.3.3.2 Definition 2

Results found for definition 2 were similar to that of definition 1.

3.3.3.2.1 Group A

Of the 263 patients with a diagnosis in CPRD alone, n=230 (87.4%) had at least one hospital admission broadly relating to psychosis while n=187 (71.1%) had a prescription for at least one antipsychotic or general mood stabilising drug. Combining these results, 95.4% (n=251) of the 263 patients identified in CPRD alone had a hospital admission, an antipsychotic therapy or both to complement their diagnosis.

3.3.3.2.2 Group B

Of the 548 patients with a diagnosis in only HES, 398(72.6%) patients had a primary care record broadly relating to psychosis while 352 (64.2%) had prescriptions for antipsychotic or other mood stabilising therapy. Combining all results, a total of 486(88.6%) patients out of the 548 patients identified as having a diagnosis in only secondary care using definition 2 had additional evidence in their primary care records to confirm the diagnosis.

3.3.3.2.3 GROUP C

By definition, 100% of the 68 patients in this group have supportive evidence.

3.3.3.2.4 Summary of validation of cohort identified using definition 2

In summary, 95% of those identified in primary care alone using the less inclusive definition had supportive evidence of the diagnosis in secondary care, while 88% of those identified in secondary care alone had supportive evidence in primary care.

Combining these results, of all 879 patients identified with definition 2, 91.5% had evidence which could substantiate their diagnosis.

Table 3-6 Cases of alcoholic psychosis with definition 2 who have supporting evidence

Alcoholic psychosis diagnosis	n	Numbers(%) with supportive evidence
CPRD only (Group A)	263	251 (95.4%)
HES only (Group B)	548	486(88.6%)
CPRD & HES (Group C)	68	68 (100%)
Total number of patients in cohort	879	805(91.5%)

3.3.4 Overall summary

Comparing the broad and restrictive definitions, there was a substantial difference in the number of cases of alcoholic psychosis that were identified. The broad definition identified 1,731 individuals while the restrictive identified a subset of 878 patients. The basic demographic characteristics of both groups were broadly similar. Additionally, for both groups, there were very similar proportions of patients for whom supportive evidence was found in the alternate database (89% vs 91.5%).

In view of the similarities between the two patient populations, I considered it therefore reasonable to conclude that the use of a less inclusive definition of alcoholic psychosis was less advantageous because it reduced the number of eligible patients (reducing available statistical power) without resulting in any noticeable improved case specificity. Therefore, the cohort of patients identified using definition 1 (more inclusive) is used for the studies on alcoholic psychosis reported in chapters 6 and 7. It is worth noting that it might have been possible to identify more supportive evidence of diagnosis from the free text fields in the GP medical records. However it was not possible to do this for this thesis as free text records were not available, nor was there funding to purchase them.

3.4 Defining study outcomes

3.4.1 Primary care consultations

To permit the description of patients' primary care encounters, all consultation records at any time period prior to diagnosis/pseudo-diagnosis date were extracted from the clinical file of patients.

Each consultation record has a "consultation type" field which can be used to define the location where a consultation took place. Using this information consultations were categorized into two groups:

- 1) Consultations involving direct contact between the patient and clinician: this includes consultations coded to have taken place in a GP surgery either during the day or during "out-of-hours" time periods
- 2) Consultations in which there was only indirect contact e.g. consultations coded to have occurred over the telephone.

Consultations included in the study were defined as those in which there was a direct contact between a clinician and a patient. This definition used in this thesis is based on a pragmatic assumption that indirect encounters do not present practitioners with opportunities to intervene or screen for alcohol misuse. Based on this definition, only consultations classified as being direct were retained in the study dataset.

3.4.2 Hospital admissions

All hospital admission dates (and corresponding admission diagnoses) at any time point in the HES record for all patients were extracted for the purpose of examining patient encounters with secondary care. Where there were any hospital admissions with missing admission dates, these were excluded from the study dataset. Additionally, admissions with inconsistent dates e.g. an admission where the discharge dates preceded the admission dates or admissions without discharge dates were also excluded.

3.4.3 Alcohol records

Within CPRD, information on different aspects of alcohol use is available within both the additional and clinical files. The additional file contains information on self-reported units of alcohol consumed per week while Read codes which relate to alcohol use, alcohol interventions and also unit consumption are contained within the clinical file (See Appendix 5 for codes relating to alcohol use). Information from both files was extracted for all individuals within the study population to define alcohol related outcomes. Overall, there were four broad types of alcohol data available (Figure 3-2).

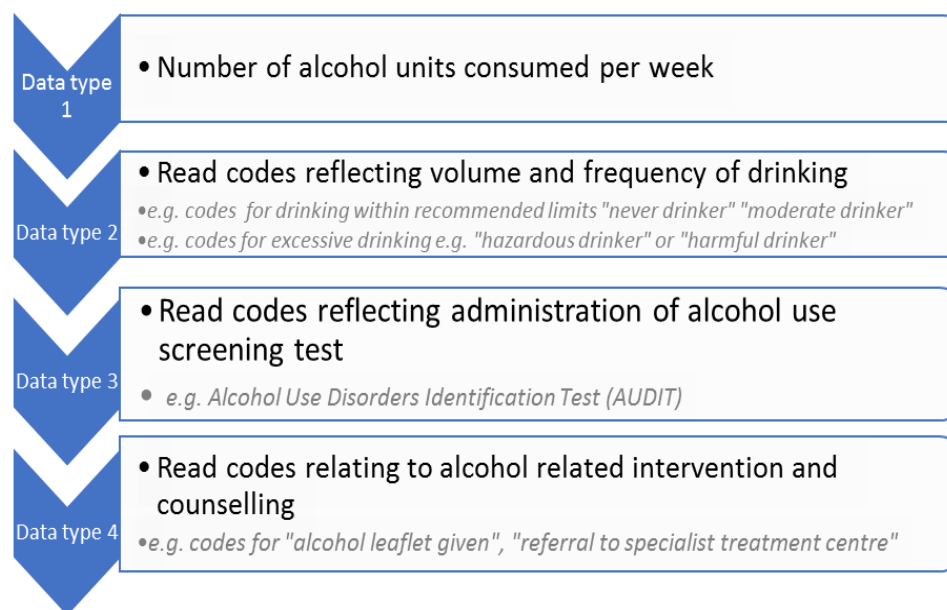


Figure 3-2 Alcohol use records available in CPRD

Patients with records relating to data type 1, 2, or 3 were classified to have had their alcohol use recorded and subsequently classified into four groups: never, moderate or harmful or hazardous drinkers using a combination of all the extracted alcohol related data.

- Never drinkers: defined as those without a drinking history or those with a record of "never drinker"
- moderate drinkers: defined as men and women who drank below 21 and 14 units respectively, or those with a Read code for moderate drinking
- Hazardous drinkers: defined as men and women drinking between 21-50 units and 14-35 units respectively, or those with a relevant read code for hazardous drinking
- Harmful drinkers: defined as men and women drinking above 50 and 35 units respectively, or with a relevant read code.

Most Read codes indicating heavy drinking were incompletely sensitive to distinguishing between harmful and hazardous drinkers. Hence for most of the results in this thesis, hazardous and harmful drinkers were grouped together.

Where a patient had only alcohol records that did not specify consumption frequency and volume e.g. beer drinker, wine drinker they were assigned an “unclear” alcohol consumption status. Where patients had multiple alcohol related records, the highest level of consumption was used to assign an alcohol consumption status. Although this categorisation using the highest ever alcohol consumption may result in some misclassification bias whereby it would not be possible to distinguish between previous or current exposure to alcohol, the status derived from this method, together with any other documented information on alcohol problems that patients may have had improves the reliability of the classification of whether patients were ever recognized to be drinking heavily prior to the diagnosis date (or pseudo-diagnosis date for the control population).

3.4.3.1 Brief alcohol intervention

Where patients had any medical code for an alcohol related intervention (records relating to data type 4) at any point in their medical record, the following categories were used 1) brief or extended advice given 2) referral to alcohol specialist service 3) brief advice given with referral.

3.5 Definition of covariates

3.5.1 Age

For the studies in this thesis, age was defined at date of diagnosis for cases and at date of pseudo-diagnosis for the control population. It was then categorized into groups as necessary for individual studies (as described in the methods section for each study).

3.5.2 Smoking status

To define smoking behaviour of patients, all data on smoking from the additional file in CPRD and all medical codes relating to smoking were extracted (see Appendix 5 for a code list for smoking). Smoking was categorized into three groups: non-smoker, smoker and ex-smoker. For individuals who had more than one smoking related record, the most recent smoking behaviour recorded before diagnosis or pseudo-diagnosis date was selected.

Chapter 4

4 Healthcare utilisation and recording of alcohol status and interventions prior to alcoholic cirrhosis diagnosis

4.1 Introduction

This chapter describes the study conducted to examine healthcare utilisation, alcohol use assessment and alcohol use interventions in men and women in the UK that eventually develop alcoholic cirrhosis, in comparison to a control population. It gives a brief background to the study and goes on to briefly describe the methods of the study. It then presents the results for healthcare utilisation and alcohol assessment and interventions (overall, and for men and women separately). The chapter concludes with a discussion of what the results imply and how it fits in with current literature. The findings described in this chapter have been published in a peer-review journal and the paper is included in Appendix 7.

4.1.1 Background

As described in the Chapter 1, mortality and incidence from alcoholic cirrhosis has increased in the past 30 years and relatively little attention has been given to understand healthcare utilisation patterns of high risk patient groups who develop the disease, although this has important implications for how the disease can be prevented using potentially effective and recommended brief interventions. Moreover, there is paucity of data on both how often alcohol use is asked about and how often brief intervention is performed in this patient group.

The occurrence of alcoholic cirrhosis is generally believed to require around 10 to 20 years of “heavy” drinking to be established(62,66,81,175). Identifying opportunities for

identification and intervention in this particularly high-risk population is therefore important as they represent a group of patients whose disease is entirely attributable to alcohol(4) and where most harm might be avoided through early identification of alcohol misuse. The aim of the study was twofold:

- 1) To estimate primary and secondary care use among men and women in the UK who later develop alcohol related cirrhosis in comparison to the general population.
- 2) To estimate the extent to which alcohol use and alcohol brief interventions were documented for men and women with alcoholic cirrhosis in comparison to the general population.

4.2 Methods

The study data was obtained from the Clinical Practice Research Datalink (CPRD) and Hospital Episodes Statistics (HES) database. Both datasets are described in detail in Chapter 2.

4.2.1 Study population

The study population comprised of incident cases of alcoholic cirrhosis between 1997 and 2012 and a control population frequency matched on age and General practice as described in Chapter 3. Briefly, all cases of alcoholic cirrhosis were identified using previously validated codes for alcoholic cirrhosis. Each patient was assigned a diagnosis date which was the date of the first code for alcoholic cirrhosis in either primary or secondary care. A total of 10 control patients without any record for which the differential diagnosis could have been alcoholic cirrhosis (i.e. unspecified cirrhosis or oesophageal varices) were selected for each patient with cirrhosis by frequency matching on age (± 5 years) and GP practice.

4.2.2 Observation period

Patients entered the study on any of the following dates: (i) the start of the linked dataset (1st April 1997), (ii) the date a patient registered with a GP practice, or (iii) the date when the practice attained an acceptable level of data recording (up to standard date), whichever came first. The study ended on the date of diagnosis for cases or pseudo-diagnosis date for controls.

4.2.3 Study variables

4.2.3.1 *Primary and secondary care usage*

Healthcare use was defined and explored using the method described in Chapter 2. Briefly, for each patient, all direct contacts with primary care and admissions to secondary care during the study period were identified from CPRD and HES respectively. The corresponding date of each contact was extracted and used to assign each event to the year in which it occurred counting back from the diagnosis/pseudo-diagnosis date (that is consultations and hospital admissions were coded as occurring in the 1st, 2nd, 3rd...10th year before diagnosis of cirrhosis). If a patient had more than one consultation within a day (whether during the day, or during out-of-hours), only one consultation for that day was counted. Primary care consultations recorded as occurring during the same period as a patient was hospitalized were excluded to avoid double counting of opportunities.

4.2.3.2 *Alcohol related outcomes*

Using all alcohol related records available within patient files (described in detail in chapter 2), patients who had had a previous alcohol use assessment, and patients with a record of an intervention were identified. All other patients who had no screening or intervention records were labelled as 'no recorded data'.

4.2.4 Other variables

Information on sex and age, were extracted from patients' CPRD records as described in section 3.4. Age was categorized into five age bands of 18–44, 45–54, 55–64, 65–74 and ≥ 75 years.

4.2.5 Statistical analyses

Proportions and means were used to describe the study population characteristics and differences between cases of alcoholic cirrhosis and the control population were tested for using Chi squared tests.

Rates of healthcare service utilisation were calculated for men and women for the entire study period, and for each year (yearly) leading up to diagnosis. Excesses in healthcare use in men and women with alcoholic cirrhosis were calculated as the absolute difference in rates between cases and the corresponding control population. Poisson regression was used to estimate rate ratios between cases and controls with 95% Confidence Intervals (95% CI). Test for interaction between sex and primary care consulting rates was carried out by fitting an interaction term in a Poisson regression model and conducting a likelihood ratio test (LRT) at a significance level of $p < 0.05$. A similar model was fitted using hospital admission rates.

To examine alcohol use enquiry and intervention delivery, the proportion of patients with both outcomes was examined by age and sex and tested for interactions using interaction terms and likelihood ratio tests in logistic regression models. Logistic regression was used to calculate the odds (95% CI) of both outcomes in people with alcoholic cirrhosis compared to controls for men and women separately. Age and consulting rate were then included in the regression models as potential confounding variables (based on theoretical plausibility) to obtain adjusted ORs.

Where possible, regression models were refitted applying the generalized estimating equation (GEE) approach with exchangeable correlation structure to test for heterogeneity with GP practices.

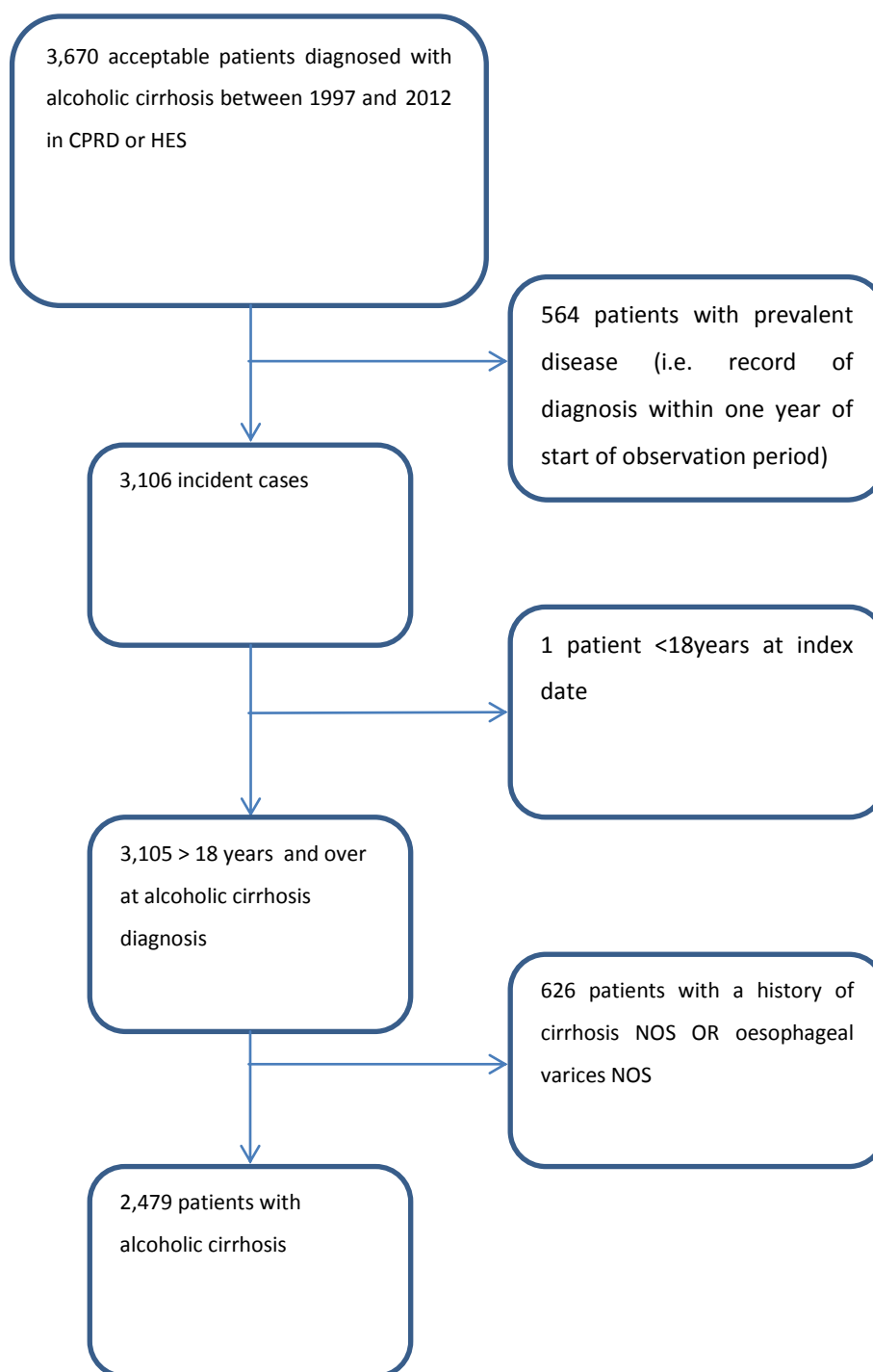
Due to the small number of patients contributing data more than 10 years before diagnosis, yearly consultation rates, rate ratios and rate differences were only estimated for the 10 year period prior to diagnosis/pseudo-diagnosis. As previously

stated all analyses were conducted using the statistical software Stata as already stated in Chapter 2.

4.3 Results

A total of 3,670 patients diagnosed with alcoholic cirrhosis between 1997 and 2012 were initially identified (Figure 4-1). After applying the study's exclusion criteria (excluding patients that were less than 18 years of age at diagnosis, patients with a history of cirrhosis "Not Otherwise Specified (NOS)" or oesophageal varices, and those diagnosed within a year of their registration) 2,479 cases remained. These were frequency matched with 10 controls each, giving a total of 27,279 patients for analysis (2,479 cases and 24,790 controls).

Figure 4-1 Selection of the patient population



4.3.1 Population characteristics

Table 4-1 shows the baseline characteristics of the population. The median observation period for people with alcoholic cirrhosis was 5.7 years before diagnosis, whilst that of the control population was 4.6 years. The average age at diagnosis of cirrhosis for cases was 55.6 years and there were more men than women in the case population (67% of cases were men).

Table 4-1 Basic characteristics of cases of alcoholic cirrhosis and the control population

	Cases (n= 2,479)	Controls (n = 24,790)
Age at diagnosis(years)		
Mean(SD)	55.6 (11.7)	55.4 (12.4)
Age group (n, %) ¹		
18-44	419(16.9)	5,027(20.3)
45-54	750(30.3)	6,772 (27.3)
55-64	753(30.4)	7,222 (29.1)
65-74	403 (16.3)	4,027 (16.2)
≥ 75	154(6.2)	1,742 (7.0)
Observation time(years)		
Median(IQR)	5.7 (3.0 – 9.2)	4.6(2.4 – 7.9)
Sex ¹		
Male	1,660(67.0)	12,453 (50.2)
Female	819 (33.0)	12,337 (49.8)
¹ Chi squared tests p value < 0.001		

4.3.2 General practice consultations before diagnosis

Figure 4-2 and table 4-2 show sex-stratified rates of primary care utilisation with rate differences and rate ratios comparing patients with alcoholic cirrhosis to the control population.

Compared to the control population, patients with alcoholic cirrhosis visited primary care more frequently (overall consultation rate per person year, cases: 9.1, controls: 5.9; IRR 1.52, (95% CI 1.51 to 1.53)), at an average excess of 3.0 consultations per person year. Greater excess consultation rates were found among men with an overall average excess of 4 consultations per person year, compared with 2.7 excess consultations for women (LRT *p* value for interaction between sex and consultation rate: <0.001). Modest changes in the number of excess consultations were observed between 10 and 5 years prior to diagnosis (1.6 to 2.9 for men, 1.1 to 2.1 for women) with a more rapid rate of change observed from 4 years to 1 year prior to diagnosis (8.5 and 7.7 excess consultations in the year prior to diagnosis for men and women respectively).

Figure 4-2 Yearly primary care consultation rates per person-year prior to alcoholic cirrhosis diagnosis

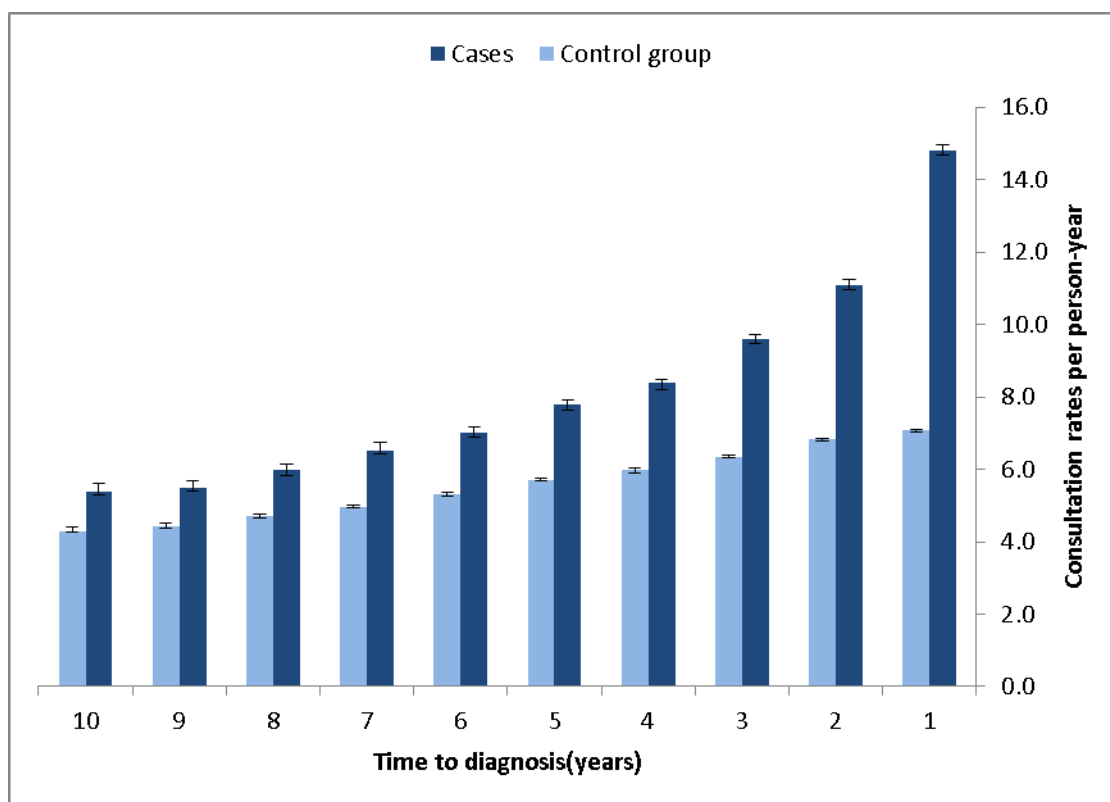


Table 4-2 Overall and yearly primary care consultation rates and rate ratios of cases of alcoholic cirrhosis and controls

	Overall				Males				Females			
	Cases	Controls	Excess	IRR(95% CI)	Cases	Controls	Excess	IRR(95% CI)	Cases	Controls	Excess	IRR(95% CI)
Overall study period												
	9.1	5.9	3.0	1.51(1.50-1.52)	8.8	4.8	4.0	1.80(1.78-1.81)	9.7	7.0	2.7	1.36(1.35-1.38)
Time to diagnosis												
1	14.8	7.1	7.7	2.09(2.07-2.11)	14.4	5.9	8.5	2.43 (2.39- 2.46)	15.5	8.2	7.3	1.88(1.85-1.92)
2	11.1	6.8	4.3	1.62(1.60-1.64)	10.9	5.8	5.1	1.89 (1.86-1.92)	11.5	7.9	3.6	1.45(1.42-1.48)
3	9.6	6.4	3.2	1.51(1.49-1.53)	9.5	5.2	4.3	1.81(1.78-1.85)	9.8	7.4	2.4	1.31(1.27-1.34)
4	8.4	6.0	2.4	1.39(1.37-1.41)	8.2	4.8	3.4	1.70(1.66-1.74)	8.7	7.1	1.6	1.20(1.17-1.24)
5	7.8	5.7	2.1	1.36(1.33-1.38)	7.5	4.6	2.9	1.64 (1.60-1.68)	8.2	6.9	1.3	1.20(1.16-1.24)
6	7.0	5.3	1.7	1.33(1.29-1.36)	6.9	4.2	2.7	1.64 (1.58-1.68)	7.5	6.4	1.1	1.15(1.11-1.20)
7	6.5	4.9	1.6	1.32(1.29-1.36)	6.1	3.8	2.3	1.61 (1.56-1.66)	7.5	6.1	1.4	1.22(1.18-1.28)
8	6.0	4.7	1.3	1.27(1.24-1.31)	5.4	3.6	1.8	1.51 (1.45-1.57)	7.1	5.8	1.3	1.21(1.17-1.27)
9	5.5	4.4	1.1	1.25(1.20-1.29)	4.9	3.4	1.5	1.43 (1.36-1.49)	6.7	5.4	1.3	1.23(1.18-1.30)
10	5.4	4.3	1.1	1.25(1.21-1.30)	4.9	3.3	1.6	1.52 (1.44-1.59)	6.4	5.4	1.0	1.19(1.12-1.26)
Likelihood ratio test p value for the interaction between sex and consultation rates, with adjustment for age: <0.0001												

4.3.3 Hospital admissions before diagnosis

Figure 4-3 and Table 4-3 show sex-stratified rates of hospital admission with rate differences and rate ratios comparing patients with alcoholic cirrhosis to the control population. The overall rate of admission was twice as high for patients with alcohol cirrhosis than for their controls (admission rate per 10-person years, cases: 5.5, controls: 2.2; IRR 2.49, (95% CI 2.42 to 2.54)). The greatest excesses were again found amongst men with an average excess of 3.7 hospital admissions per 10-person years during the entire study period compared with 2.7 excess admissions for women (LRT p value for interaction between sex and admission rate: <0.001). As with primary care consultations, for each year before diagnosis a gradual increase in rates of admission was seen, with excesses higher in men than women in all years.

Figure 4-3 Yearly hospital admission rates per 10 person-years prior to alcoholic cirrhosis diagnosis.

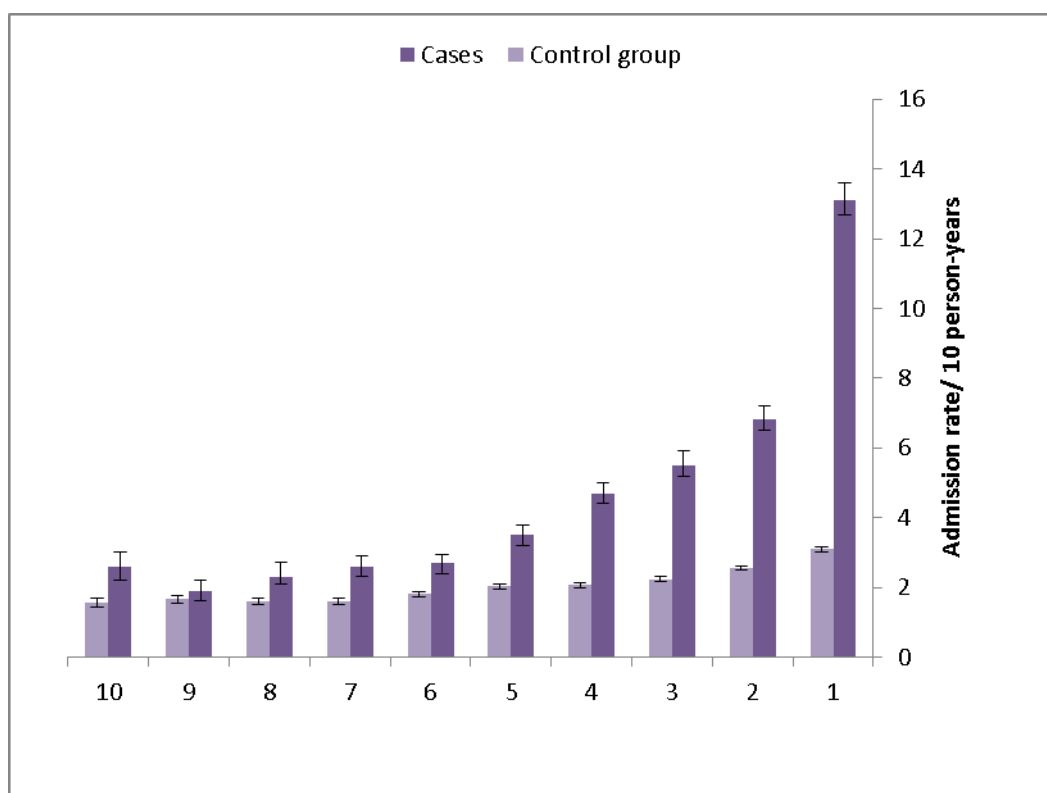


Table 4-3 Overall and yearly admission rates (per 10 person years) and rate ratios of cases of alcoholic cirrhosis and controls

	Overall				Males				Females			
	Cases	Controls	Excess	IRR(95% CI)	Cases	Controls	Excess	IRR(95% CI)	Cases	Controls	Excess	IRR(95% CI)
Overall study period												
	5.5	2.2	3.3	2.49(2.42-2.54)	5.8	2.1	3.7	2.82(2.73-2.90)	5.0	2.4	2.6	2.09(2.01-2.19)
Time to diagnosis												
1	13.1	3.1	10	4.23(4.06-4.41)	13.5	2.9	10.6	4.64(4.40-4.89)	12.2	3.3	8.9	3.73(3.48-3.99)
2	6.8	2.6	4.2	2.67(2.53-2.83)	7.1	2.4	4.7	2.92(2.72-3.13)	6.2	2.7	3.5	2.32(2.11-2.56)
3	5.5	2.2	3.3	2.47(2.32-2.64)	6.1	2.1	4	2.89(2.67-3.14)	4.4	2.4	2	1.86(1.65-2.10)
4	4.7	2.1	2.6	2.27(2.10-2.45)	5.1	1.9	3.2	2.63(2.39-2.89)	3.7	2.2	1.5	1.73(1.50-1.99)
5	3.5	2.0	1.5	1.71(1.56-1.88)	3.5	1.9	1.6	1.88(1.67-2.11)	3.3	2.2	1.1	1.52(1.29-1.79)
6	2.7	1.8	0.9	1.47(1.31-1.65)	2.8	1.6	1.2	1.77(1.53-2.04)	2.4	2.0	0.4	1.17(0.95-1.44)
7	2.6	1.6	1	1.63(1.44-1.86)	2.8	1.2	1.6	2.28(1.95-2.69)	2.1	1.9	0.2	1.09(0.86-1.38)
8	2.3	1.6	0.7	1.49(1.29-1.73)	2.4	1.3	1.1	1.82(1.50-2.19)	2.3	1.9	0.4	1.26(0.98-1.61)
9	1.9	1.7	0.2	1.12(0.93-1.34)	1.8	1.6	0.2	1.19(0.94-1.49)	1.9	1.8	0.1	1.08(0.80-1.46)
10	2.6	1.6	1	1.64(1.36-1.96)	2.3	1.3	1	1.76(1.37-2.24)	3.1	1.8	1.3	1.69(1.29-2.22)
Likelihood ratio test p value for the interaction between sex and consultation rates, with adjustment for age: <0.0001												

4.3.4 Alcohol use records

Alcohol consumption records (including records of being a non-drinker) were available for 2,088 (84.2%) cases and 16,752 (67.6%) controls. On average, 52% of cases had their first alcohol use record more than 5 years before cirrhosis was diagnosed, 27% had theirs between 2 and 5 years before diagnosis, while for 9% it was within the year before diagnosis (Table 4-5).

Substantially more cases (60.0%, n=1,507) than controls (9.5%) had a record of harmful or hazardous drinking (Table 4-4). Of the 1,507 cases, 43% had this problem drinking record more than 5 years before cirrhosis was diagnosed, 31% had theirs between 2 to 5 years before diagnosis while 13% were identified as harmful or hazardous drinkers only in the year before diagnosis (Table 4-6). On average, the time between the first record of hazardous or harmful drinking and the diagnosis of alcoholic cirrhosis for all patients combined was 4.2 years (IQR 1.9 to 7.5 years).

As shown in Table 4-7, compared to the control population, men with alcoholic cirrhosis were more likely to have a record of their alcohol use than women (85% compared to 82%, p value < 0.001). Women were less likely to have alcohol use records with increasing age, but the reverse was true for men (Table 5). After adjusting for the effect of age and consulting rate, the odds of having an alcohol consumption record remained higher for men at OR 1.96 (95% CI, 1.7 to 2.3, p value <0.001)] than women [OR 1.63 (95% CI, 1.4 to 1.8, p <0.001)] (Table 4-7).

Table 4-4 Proportion of patients who had any alcohol use record during the pre-diagnosis/ pseudo-diagnosis period.

Variable	Cases (n, %)	Controls (n, %)
Patients with records of alcohol use ¹		
Alcohol use status recorded	2,088(84.2)	16,752(67.6)
Never	48(1.9)	2,347(9.5)
Moderate	377(15.2)	11,374(45.9)
Hazardous/harmful	1,507(60.7)	2,344(9.5)
Unclear	156(6.3)	687(2.8)
No data recorded	391(15.8)	8,038(32.4)
¹ Chi squared tests p value <0.001		

Table 4-5 Time between earliest record of alcohol use and alcoholic cirrhosis diagnosis/pseudo-diagnosis

	Cases n=2,088 (%)	Control group n=16,752 (%)
Time to diagnosis or pseudo-diagnosis (years)		
=<1year	188 (9.0)	993 (5.9)
>1-2years	226 (10.8)	2,410 (14.4)
>2-5years	579 (27.7)	4,903 (29.3)
>5years	1,095 (52.4)	8,446 (50.4)

Table 4-6 Timing between earliest harmful/hazardous record and disease diagnosis or pseudo-diagnosis

	Cases n=1,507 (%)	Control group n=2,344 (%)
Time to diagnosis/pseudo-diagnosis in years		
=<1year	193 (12.8)	226 (9.6)
>1-2years	189 (12.5)	346 (14.8)
>2-5years	465 (30.9)	723 (30.8)
>5years	660 (43.8)	1,049 (44.8)

Table 4-7 Proportion of patients with any alcohol use record stratified by sex and age with OR and 95 CIs

	Cases n=1,660	Controls n=12,453	OR(95% CI)	Cases n= 819	Controls n=12,337	OR(95% CI)
	Males			Females		
Overall	1,414(85.2)	8,103(65.1)	1.96(1.7-2.3)* ⁺	674(82.3)	8,649(70.1)	1.63(1.4-1.8)* ⁺
Age at diagnosis(years)						
18-44	228(83.2)	1,571(60.7)	3.2(2.3-4.5)	131(90.3)	1,760(72.2)	3.6(2.1-6.3)
45-54	412(83.7)	2,228(63.8)	2.9(2.3-3.8)	216(83.7)	2,269(69.2)	2.3(1.6-3.2)
55-64	447(86.8)	2,461(66.3)	3.3(2.6-4.4)	192(80.7)	2,476(70.6)	1.7(1.3-2.4)
65-74	239(87.6)	1,344(68.9)	3.2(2.2-5.6)	103(79.2)	1,447(69.6)	1.6(1.1-2.6)
≥ 75	88(83.0)	499(70.1)	2.1(1.2-3.6)	32(66.7)	697(67.7)	0.9(0.5-1.7)
*OR adjusted for age and consulting rate of patients						
+ Likelihood ratio test p value < 0.001						
n also includes patients with a record of NOT drinking						

4.3.5 Alcohol use interventions

Electronic coded recording of an offer of an intervention was found for 22.8% (n=565) of cases (Table 4-8). Out of these n=481 had a harmful drinking record putting the intervention rate among those with a harmful drinking record at 31.9% (481/1507). Among the control population, the proportion with intervention records was 4.7% (n=1,151). Overall, the most commonly documented alcohol related intervention for both cases and controls was “brief advice”.

As shown in Table 4-9, alcohol intervention was low among men and women with alcoholic cirrhosis (23% vs 22%, $p < 0.001$). Both sexes were less likely to receive interventions with increasing age, but the lowest proportions were found among women aged 65 years and above (Table 6). After adjusting for age and differences in consulting rate, women with alcoholic cirrhosis (Adjusted OR 5.8, 95% CI (4.8 to 7.0), $p < 0.001$) were more likely than men (Adjusted OR 4.3, 95% CI (3.7 to 4.9), $p < 0.001$) to have an intervention record when compared to the control population (Table 4-9).

Table 4-8 Proportion of patients with any record of alcohol brief intervention or referral for specialist treatment during the pre-diagnosis/pseudo-diagnosis period

	Cases (n, %)	Controls (n,%)
Intervention (n, %)¹		
Recorded offer of an intervention	565(22.8)	1,151(4.7)
Brief or extended intervention given	520(20.9)	1,142(4.6)
Referral given	28(1.1)	7(<0.1)
Brief intervention and referral given	17(0.7)	2(<0.1)
No data recorded	1,914(77.2)	23,639(95.3)
¹ Chi squared test p value p<0.001		

Table 4-9 Proportion of patients with any alcohol intervention record stratified by sex and age and OR and 95% CIs

	Cases n=1660	Controls n=12,453	OR(95% CI)	Cases n= 819	Controls n=12,337	OR(95% CI)
	Males			Females		
Overall	385(23.2)	642(5.2)	4.3(3.7-4.9)* ⁺	180(22.0)	509(4.1)	5.8(4.7-6.9) * ⁺
Age at diagnosis						
18-44	57(20.8)	86(3.3)	7.6(5.3-11.1)	45(31.0)	84(3.4)	12.6(8.2-19.4)
45-54	110(22.4)	170(4.9)	5.6(4.3-7.4)	65(25.2)	144(4.4)	7.3(5.2-10.3)
55-64	135(26.2)	239(6.4)	5.2(4.1-6.6)	45(18.9)	147(4.2)	5.3(3.7-7.7)
65-74	68(24.1)	114(5.9)	5.3(3.8-7.5)	21(16.15)	91(4.4)	4.2(2.5-7.1)
≥ 75	15(14.2)	33(4.6)	3.4(1.8-6.5)	4(8.3)	43(4.2)	2.1(0.7-6.1)
*OR adjusted for age and consulting rate of patients						
+likelihood ratio test p value < 0.001						

4.4 Discussion and interpretation

4.4.1 Main findings

The findings of this study show that patients with alcoholic cirrhosis had a greater number of contacts with both primary and secondary healthcare during the years leading up to their diagnosis of alcoholic cirrhosis than the general population. This excess was more pronounced in men than women and was exceptionally high in the 5 year period before diagnosis to suggest that this may be the window of opportunity to identify and treat such patients. The proportion of men with alcoholic cirrhosis who had been asked about their alcohol use was greater than that of women. However, by contrast, women were more likely to be offered a brief alcohol intervention or referral even after controlling for age and consulting rate. These findings suggest that for people who go on to develop alcoholic cirrhosis, there are potentially missed opportunities for earlier identification and treatment of alcohol misuse, particularly in men. It also highlights potential inequalities in favour of women with respect to having an offer of an alcohol related intervention. Another inequality identified was with respect to age. Although the offer of brief interventions was generally low, those in the older age groups were less likely than the younger age groups to have received an offer of an intervention prior to the diagnosis of their disease.

4.4.2 Strengths and limitations

This is the first longitudinal study to describe primary and secondary healthcare use (a proxy for intervention opportunities) among an important group of hazardous/harmful drinkers compared with a representative general population control group. The use of the linkage between primary and secondary care data has enabled the identification of a comprehensive population of patients with alcoholic cirrhosis as it has been previously reported that using either primary care or secondary care data alone significantly underestimates the number of patients with this condition(172). The potential effect of age and general practice on consulting rates has been minimised by frequency matching cases to controls on these variables. The differential contribution time of patients to the study has been taken account of by calculating rates using the person time approach. This methodology provides the assurance that increases in consultation or admission rates in the years closer to diagnosis are not as a result of more patients contributing data within those years.

Certain limitations should however be considered in the interpretation of our findings. With regard to alcohol use recording/interventions, it is likely that doctors have screened patients for alcohol use and/or delivered interventions but have not made a specific record of this within the coded data system. Hence the reported proportion of patients who were asked about their alcohol use or offered interventions is likely to be an underestimate. However, the magnitude of the differences identified between men and women and across age groups is unlikely to be explained by this potential bias alone, as it seems unlikely that there would be differential recording among cirrhosis patients based on sex and age. It was not possible to adjust the study findings for some variables (e.g. socioeconomic status, and ethnicity) that may have a confounding effect on sex differences in health service utilisation, and this was because these measures

were not available within the dataset for the study population at the time the study was conducted. Additionally, although steps were taken to account for any clustering effects within GP practices in the analysis, there was no information of other factors within practices which may affect the extent of intervention delivery or referral e.g. the availability of specialist treatment centres in the community where a practice is located, practitioners willingness to discuss alcohol use or practitioners views on the threshold of drinking which constitutes a problem. Given that it is not possible to know the extent to which these unmeasured factors may have biased the study findings and that no other observational study has explored such outcomes for patients with alcoholic cirrhosis to date, future studies may wish to consider approaches that can determine the magnitude of the potential impact of such confounders.

4.4.3 Comparison with previous studies

Only two cross sectional studies have previously reported healthcare use of patients with alcohol problems and their findings are broadly consistent with the results presented here in that they highlight patients with alcohol problems are often in contact with healthcare services(80,81). While the absence of control groups and small sample sizes may make the generalizability of these studies difficult, the use of an extremely large representative database in this study provides the opportunity for more generalizable estimates. Far less data are available on sex comparisons of healthcare utilisation in patients with alcohol problems. Most studies examining sex differences in the use of health care services have been on the general population (176–180) or in patients with specific symptoms such as pain (181,182). In line with most of these studies (176–180,183), higher absolute rates of consultation was found in women compared to men. However, in relative terms, when men and women with alcoholic cirrhosis were examined in comparison to general population, the increase in health service use associated with the disease was more dramatic in men than women. In terms of alcohol use recording and intervention delivery, consistent with the study results, a number of studies have reported that the implementation of brief alcohol interventions within healthcare settings is generally slow in the UK as well as internationally (144,184–186).

4.4.4 Implications

The present study suggests that there are several opportunities, particularly in men, for the earlier identification and treatment of alcohol misuse. That a high proportion of people had an alcohol use record is encouraging and suggest that GPs in the UK inquire about alcohol consumption during healthcare visits. However results on interventions

generate some concern. If true, the low rate of intervention identified in this study cannot be explained by low access to healthcare services. This finding is also not entirely explained by a low drinking problem identification rate, because at least two-thirds (60.7%) of cases had had at least one problem drinking record four years prior to alcoholic cirrhosis diagnosis. The most plausible alternative explanations are that there may be a failure to record treatment of alcohol problems in primary care, that appropriate treatment services are not consistently available or that treatment of alcohol problems might truly be suboptimal.

As documented in previous studies, the reasons why the delivery of brief alcohol interventions may be suboptimal include lack of time, lack of workplace support, poor financial reimbursement and feelings of inadequacy by healthcare staff(144,145,148,187). In general, educating healthcare professionals on the importance of universal screening and early treatment of at risk drinkers may lead to an improvement in the current extent of intervention delivery. However, it may be important for policymakers to consider integrating screening and brief alcohol interventions into a nationwide pay for performance initiative such as the Quality and Outcomes framework (QOF) scheme. QOF, introduced in 2004, provides financial incentives for UK general practices that meet certain care/quality criteria. Introduction of the QOF led to an increased ascertainment of smoking behaviour and documentation of care provided to smokers by practitioners (36–38). Ascertainment of alcohol use is now part of the NHS health checks programme in England but typically, this component of the check is not systematically quality assured or paid for separately to the health check as a whole (39). A pilot study carried out between 2008 and 2011 in 30 General practices in north-west London, UK showed that a QOF ‘extra’ scheme to tackle alcohol use in certain patient groups led to an increase in screening for alcohol misuse among all patients, and had a spill-over effect even in those not covered by the

scheme (40). This evidence not only shows the potential of such a scheme, but also favours the suggestion that systematically rolling out a pay for performance initiative for alcohol misuse at a national level may be the next important step to improve how alcohol misuse is addressed within healthcare settings, and reduce the potential inequity in alcohol related care identified in this study.

Another aspect of these results for which there are important implications is the finding that women, especially those of younger ages, were more likely than men to receive brief alcohol interventions. These findings need further exploration. However, if replicated in future, it would imply that strategies to treat alcohol problems on a population level may be undermined as men make up a significant proportion of the population of people with alcohol use disorders and are more likely to drink alcohol in excess of women (188,189).

4.4.5 Conclusions

The findings of the study show a higher excess of healthcare use in men than women prior to alcoholic cirrhosis. While a high proportion of patients were asked about their alcohol use during these healthcare visits, few patients had records of interventions and men were less likely to receive interventions than women. I acknowledge that recording biases may partly explain the low rates of intervention identified in this study. However, the identification of high risk patients relies heavily on doctors having access to both current and past records of patients' alcohol use; hence recording biases in itself represents a key aspect of brief intervention delivery which needs to be highlighted if the treatment of alcohol problems is to be improved. Given the potential effectiveness of screening and alcohol brief interventions to reduce risky drinking

behaviour and the need to reduce alcohol problems at a population level, these findings should encourage healthcare professionals to screen for alcohol use and use brief interventions more often and policy makers to direct more effort towards integrating these interventions into clinical practice.

Chapter 5

5 Alcohol attributable morbidities present in patients before the diagnosis of alcoholic cirrhosis

The aim of this study was to investigate the burden of alcohol-attributable morbidities in patients before the diagnosis of alcoholic cirrhosis, in order to better understand the high consulting trends in these patients identified in the previous chapter and to potentially identify conditions or diseases which may allow earlier, more targeted interventions.

5.1 Introduction

As previously described, alcoholic cirrhosis is believed to take several years of heavy drinking to become established. During this time people are likely to present to their family doctor/General Practitioner or to hospital emergency departments for conditions that are related to alcohol, but not necessarily directly related to cirrhosis. This is not dissimilar to the situation where patients persistently present to primary care with smoking related symptoms e.g. weight loss and angina-like chest pain several years before they are diagnosed with lung cancer (190–192). Knowledge of such symptoms that are associated with the cause of a disease, rather than a disease itself, has been used in the past as a proxy for risk stratification of individuals for targeted interventions (193,194). Such stratification could result in improvement in early diagnosis rates and reduction in mortality from chronic diseases which are otherwise extremely problematic both in terms of prognosis and complications if identified at a late stage (195).

For alcoholic cirrhosis however there is lack of information on the likely burden of alcohol related morbidity that may be present in patients before cirrhosis diagnosis.

The morbidities believed to be associated with alcohol are many and include some malignancies, some cardiovascular diseases, epilepsy, unintentional and self-harm injuries (4). However, limited studies have explored the occurrence of these morbidities in patients with cirrhosis specifically during the period prior to diagnosis. One prior small study of 94 people with alcoholic liver disease was identified which reported the occurrence of limited categories of morbidities (injuries, seizures, oral malignancy and digestive diseases) as a secondary study outcome(80) but there was no comparison population in this study and so the relevance of reported morbidities remain unclear.

Given the impact of alcoholic cirrhosis on life expectancy(172) and the potential benefits of preventative interventions, there is a clear need to better understand which morbidities may be present in patients before the disease is diagnosed. More so given that there is some literature suggesting that fibrosis can be reversed if drinking is stopped early enough(56). The aim of this study therefore was to estimate the burden of diseases that are reported to be at least partly attributable to alcohol in patients during the time leading up to a diagnosis of cirrhosis, in comparison with the general population.

5.2 Methods

5.2.1 Dataset and study population

This was a case-control study using primary healthcare data from Clinical Practice Research Datalink (CPRD) and linked hospital admissions data from Hospital Episodes Statistics (HES) database. A full description of HES and CPRD datasets has been provided in Chapter 2. The study period and population is the same as that used in chapter 4. It includes 2,479 cases of alcoholic cirrhosis and 24,790 controls frequency

matched by age and General practice selected between 1997 and 2012 from HES-linked CPRD practices.

5.2.2 Identifying partly alcohol-attributable morbidity in primary and secondary care

The list of conditions considered to be partly attributable to alcohol was based on England's national guide for alcohol-attributable fractions which has been validated against other international sources(87,196). These were:

- Mouth and oropharynx cancers (ICD-10: C00–C14)
- Oesophageal cancer (C15)
- Colon and rectal cancers (C18–C21)
- Breast cancer (C50)
- Diabetes mellitus (E10–E14)
- Epilepsy (G40, G41)
- Hypertensive disease (I10–I14)
- Ischaemic heart disease (I20–I25)
- Haemorrhagic stroke (I60–I62)
- Ischaemic stroke (I63)
- Road traffic accidents (many V codes)
- Falls (W00–W19)
- Drowning (W65–W74)
- Poisonings (X40–X49)
- Other unintentional injuries (rest of V codes plus some W, X, Y codes)
- Self-inflicted injuries (X60–X84, Y87.0)
- Violence (X85–Y09, Y87.1)
- Intentional injuries (Y35)

Read and ICD 10 codes for these conditions were used to identify people with these conditions before cirrhosis diagnosis or pseudo-diagnosis date by searching patient's primary and secondary care records respectively. Where a patient had multiple consultations or hospital admissions with a specific diagnostic code, only the earliest record was kept for this analysis. Where codes for different diseases were first entered on the same date - for example if an individual received a diagnosis code for hypertension and was also diagnosed with diabetes on the same date, both records of unique diseases were included. Each first diagnosis was grouped into one of four exposure periods as follows: within 12 months, between 13 months-2 years, between 3-5 years and between 6-10 years before diagnosis or pseudo-diagnosis date. For clarity of presentation we further grouped all diseases into categories (malignant neoplasms, diabetes, diseases of the nervous system, cardiovascular diseases, digestive diseases, and injuries) based on ICD10 chapter headings.

5.2.3 Covariates

Data on patient sex, age, smoking history and alcohol use were extracted from CPRD as described in Chapter 2.

5.2.3.1 Missing data

Missing data on smoking or alcohol use was addressed by including a "no data available" category so that such patients were not excluded from the analyses.

5.2.4 Statistical analysis

Baseline characteristics of cases and controls were described using descriptive statistics and compared via chi squared tests or t-test as appropriate. The proportions of patients that were ever diagnosed with any alcohol-attributable disease condition and

those with one, two or three or more diseases were calculated. Then, the frequency of each specific disease and each disease group among cases and controls was also calculated using the number of people identified as ever having a diagnosis as the numerator and the number of patients with alcoholic cirrhosis or controls as the denominator. Logistic regression was used to explore the association between each disease group and alcoholic cirrhosis; results are presented as odds ratios (OR) and 95% confidence intervals (CI). Further, the potential for effect modification by age and sex on this association was assessed via stratified analyses and the fitting of interaction terms in the logistic regression model; the significance of models was tested using likelihood ratio tests (LRTs), with $p < 0.05$ considered significant.

To investigate whether the occurrence of morbidities varied at different times before cirrhosis diagnosis, disease frequencies and odds ratios were recalculated for the four predefined exposure periods before diagnosis. Not all patients were included in these analyses. Restriction was applied based on completeness of follow up such that the analyses for any time period were limited to those with complete follow up. For example, only patients with a minimum of 2 years' worth of pre-diagnosis data were included in 13 months-2 year time period analyses. Likewise, only individuals with up to 5 years and up to 10 years' worth of pre diagnosis data were included in the 3-5 year and 6-10 year time periods respectively.

Additional analysis was carried out on injuries to take into account the fact that injuries are acute, people could have multiple acute injuries over time and therefore analysing only the first ever injury may underestimate the association between injuries and cirrhosis over time. For this analysis, all injury codes recorded for each patient within each predefined time period were assessed in order to identify whether a person had had a new injury in each period. A new injury was defined as a read code entered

30days (for all injury types except fractures) or 100 days (for fractures) after an initial code for the same injury. These time windows were chosen through examining of the distribution of medical codes after an initial injury event which showed that codes entered into the medical records due to repeat consultations for the same injury event levelled off around 30 days for most injures and around 90 days for fractures. Using this additional information, frequencies and odds ratios for injuries were then recalculated for each pre-defined period.

All time specific odds ratios were adjusted for age, sex and smoking status.

All analyses as previously mentioned were conducted using the statistical software Stata v12.0 (StataCorp, Texas).

5.3 Results

5.3.1 Population characteristics

As previously, the study population comprised 2,479 cases and 24,790 controls. The mean age at cirrhosis diagnosis was 55.6 years. The median observation time prior to diagnosis (or pseudo diagnosis) was higher in cases than controls: 5.7 years (IQR 3.0 - 9.2 years) and 4.6 years (IQR 2.4 – 7.9 years) respectively. Compared with controls, cases of alcoholic cirrhosis were more likely to be men, current smokers and harmful/hazardous drinkers (Table 5-1).

Table 5-1 Baseline characteristics of the study population.

	Cases n=2,479	Controls n=24,790	P value ¹
Age at diagnosis(years)			
Mean(SD)	55.6 (11.7)	55.4 (12.4)	
Age group (n, %)			
min-44	419(16.9)	5,024(20.3)	<0.001
45-54	750(30.3)	6,772 (27.3)	
55-64	753(30.4)	7,222 (29.1)	
65-74	403(16.3)	4,027 (16.2)	
≥ 75	154(6.2)	1,742 (7.0)	
Observation time(years)			
Median(IQR)	5.7(3.0 – 9.2)	4.6(2.4 – 7.9)	
Up to 12months	2,479(100.0)	24,790 (100.0)	
Up to 2years	2,151(86.8)	20,162 (81.3)	
Up to 5years	1,377(55.6)	11,422(46.1)	
Up to 10 years	482 (19.4)	3,432(13.8)	
Sex (n, %)			<0.001
Male	1,660(67.0)	12,453 (50.2)	
Female	819(33.0)	12,337 (49.8)	
Smoking status			<0.001
Non smoker	508(20.5)	9,995(40.3)	
Current smoker	1,175(47.4)	5,080(20.5)	
Ex-smoker	415(16.7)	4,543(18.3)	
Data not available	381(15.4)	5,172(20.9)	
Alcohol use status			<0.001
Data available	2,088(84.2)	16,752(67.6)	
Never	48(1.9)	2,347(9.5)	
moderate	377(15.2)	11,374(45.9)	
Hazardous/harmful	1,507(60.7)	2,344(9.5)	
unclear	156(6.3)	687(2.8)	
Data unavailable	391(15.8)	8,038(32.4)	
¹ Chi squared test p value			

5.3.2 Alcohol-attributable healthcare attendances

Table 5-2 shows the proportions of patients who presented to primary or secondary care with at least one partially alcohol-attributable condition during the study period. Nearly two thirds (58%) of cases had presented with at least one condition partially attributable to alcohol during a preceding primary care or hospital visit, compared to 29% in the control population (Table 5-2). There was a three-fold risk of patients being diagnosed later with alcoholic cirrhosis in patients presenting with any alcohol-attributable condition. Alcoholic cirrhosis risk was found to increase with increasing numbers of alcohol-attributable conditions; from over two fold (OR 2.7, 95% CI 2.5-3.0) in those with one condition to 9 fold in those with three or more conditions (OR 9.3, 95% CI 7.5-11.7).

Table 5-2 Proportion of patients with at least one partially alcohol-attributable condition at any point during the study, with OR (95% CI) comparing cases to controls.

Any GP or hospital diagnosis of partly alcohol attributable condition	Cases (n=2,479)	Controls (n=24,790)	OR(95% CI)
Yes	1,443(58.2)	7,201(29.1)	3.3(3.1-3.7)
1	909(36.7)	5,627(22.7)	2.7(2.5-3.0)
2	407(16.4)	1,343(5.4)	5.1(4.5-5.8)
3 or more	127(5.1)	231(0.9)	9.3(7.5-11.7)
No	1,036(41.8)	17,589(70.9)	

Table 5-3 shows proportions of patients seen for at least one alcohol attributable condition stratified by age and sex. When cirrhosis risks was across age groups, stronger associations with cirrhosis were found for younger patients (OR for those <45 years 6.1, 95% CI [4.9-7.5]) who had presented with an attributable morbidity compared to older patients (OR for those >75years 2.5, 95% CI [1.7-3.7]). Comparing risks by sex, no substantial difference was observed between men (OR 3.6, 95% CI [3.2-3.9]) and women (OR 3.2, 95% CI [2.8-3.7]).

Table 5-3 Proportion of patients with at least one partially alcohol-attributable condition at any point during the study, with OR (95% CI) comparing cases to controls, stratified by sex and age.

	Cases N=2,479	Controls N=24,790	Odds ratios (95% CI)
Sex			
Male			
No	690(41.6)	8,928(71.7)	-
Yes	970(58.4)	3,525(28.3)	3.6(3.2-3.9)
Female			
No	346(42.3)	8,661(70.2)	-
Yes	473(57.8)	3,676(29.8)	3.2(2.8-3.7)
Age groups			
18-44			
No	197(47.0)	4,245(84.4)	-
Yes	222(52.9)	782(15.6)	6.1(4.9-7.5)
45-54			
No	344(45.9)	1,472(21.7)	-
Yes	406(54.1)	5300(78.3)	4.2(3.6-4.9)
55-64			
No	321(42.6)	4,875(67.5)	-
Yes	432(57.4)	2,347(32.5)	2.8(2.4-3.3)
65-74			
No	133(33.0)	2,334(57.9)	-
Yes	270(67.0)	1,693(42.1)	2.8(2.2-3.5)
≥ 75			
No	41(26.6)	835(47.9)	-
Yes	113(73.4)	907(52.1)	2.5(1.7-3.7)
LRT for interaction between sex and the likelihood of presenting with an alcohol attributable condition: p =0.26			
LRT for interaction between age and the likelihood of presenting with an alcohol attributable condition: p < 0.0001			

Table 5-4 and Figure 5-1 shows age stratified proportions and ORs for each disease group. The most common ICD 10 categories among cases were injuries (35.9%), cardiovascular diseases (23.2%) and diabetes (12.8) corresponding to adjusted odds ratios of 4.0 (95% CI [3.7-4.4]), 1.6 (95% CI [1.5-1.8]) and 2.5 (95%CI [2.2-2.9]) (Figure 5-1 and Table 5-4). Digestive (6.1%) and nervous system (5.0%) diseases were relatively uncommon in absolute terms but had the highest odds ratios when comparing cases to controls at 5.4 (95% CI [4.4-6.7]) and 4.4 (95% CI [3.5-5.5]) respectively. We observed a marked variation in the magnitude of effect across age groups for most diseases. The odds of cardiovascular, nervous system, digestive diseases and injuries for instance generally decreased with increasing age, with the highest odds among those aged less than 45 years old. For malignant neoplasms and diabetes, odds were highest for those less than 45 years and for those over 75 years compared to the other age groups.

Table 5-4 Overall and age stratified proportions and odds ratios for selected comorbidities (classified by ICD 10 headings) for cases and controls

	Cases (n=2,479) n(%)	Controls (n=24,790) n(%)	OR (95% CI)		LRT p-value for age interaction
			Unadjusted	Adjusted*	
Malignant neoplasms	62(2.5)	323(1.3)	1.9 (1.5-2.6)	2.4(1.8-3.3)	0.61
18-44	4(0.9)	13(0.3)	3.7(1.2-11.5)	4.3(1.3-14.3)	
45-54	8(1.1)	47(0.7)	1.5(0.7-3.2)	1.8(0.8-4.0)	
55-64	21(2.8)	112(1.6)	1.8(1.1-2.9)	2.4(1.5-3.9)	
65-74	17(4.2)	102(2.5)	1.7(1.0-2.9)	2.0(1.2-3.5)	
≥ 75	12(7.8)	49(2.8)	2.9(1.5-5.6)	3.3(1.6-6.5)	
Diabetes	318 (12.8)	1,303 (5.3)	2.7(2.3-2.9)	2.5(2.2-2.9)	0.02
18-44	21(5.0)	65(1.3)	4.0(2.4-6.7)	4.0(2.3-6.8)	
45-54	62(8.3)	234(3.5)	2.5(1.9-3.4)	2.3(1.7-3.2)	
55-64	109(14.5)	445(6.2)	2.6(2.1-3.2)	2.4(1.9-3.1)	
65-74	75(18.6)	383(9.5)	2.2(1.7-2.9)	2.0(1.5-2.7)	
≥ 75	51(33.1)	176(10.1)	4.4(3.0-6.4)	4.2(2.8-6.3)	
Nervous system diseases	125 (5.0)	264(1.1)	4.9 (3.9-6.1)	4.4(3.5-5.5)	0.0001
18-44	43(10.3)	53(1.1)	10.7(7.1-16.3)	9.1(5.8-14.3)	
45-54	45(6.0)	72(1.0)	5.9(4.1-8.7)	5.1(3.4-7.7)	
55-64	27(3.6)	82(1.1)	3.2(2.1-5.0)	3.2(2.0-5.0)	
65-74	9(2.2)	33(0.8)	2.8(1.3-5.8)	2.2(1.0-4.7)	
≥ 75	1(0.7)	24(1.4)	0.5(0.1-3.4)	0.5(0.1-3.5)	
Cardiovascular diseases	576(23.2)	3,877 (15.6)	1.6 (1.5 -1.8)	1.6(1.5-1.8)	0.0002
18-44	36(8.6)	151(3.0)	3.0(2.1-4.4)	3.3(2.2-4.9)	
45-54	133(17.7)	605(8.9)	2.2(1.8-2.7)	2.1(1.7-2.6)	
55-64	194(25.8)	1,353(18.7)	1.5(1.3-1.8)	1.4(1.2-1.7)	
65-74	155(38.5)	1,149(28.5)	1.6(1.3-1.9)	1.5(1.2-1.8)	
≥ 75	58(37.7)	619(35.5)	1.1(0.8-1.5)	1.1(0.7-1.5)	
Digestive diseases	152 (6.1)	298 (1.2)	5.4 (4.3-6.5)	5.4(4.4-6.7)	<0.0001
18-44	36(8.6)	27(0.5)	17.4(10.4-28.9)	21.1(12.1-36.7)	
45-54	35(4.7)	62(0.9)	5.3(3.5-8.1)	5.1(3.2-8.1)	
55-64	41(5.4)	101(1.4)	4.1(2.8-5.9)	4.1(2.7-6.0)	
65-74	29(7.2)	76(1.9)	4.0(2.6-6.3)	4.1(2.6-6.5)	
≥ 75	11(7.1)	32(1.8)	4.1(2.0-8.3)	3.7(1.7-7.7)	
Injuries	891(35.9)	2,962(11.9)	4.1(3.8-4.5)	4.0(3.7-4.4)	0.008
18-44	172(41.1)	554(11.0)	5.6(4.5-7.0)	4.9(3.9-6.1)	
45-54	270(36.0)	720(10.6)	4.7(4.0-5.6)	4.3(3.5-5.1)	
55-64	237(31.5)	835(11.6)	3.5(3.0-4.2)	3.5(2.9-4.2)	
65-74	149(36.9)	500(12.4)	4.1(3.3-5.2)	4.3(3.4-5.4)	
≥ 75	63(40.9)	353(20.3)	2.7(1.9-3.8)	3.2(2.2-4.6)	

*adjusted for sex and smoking status

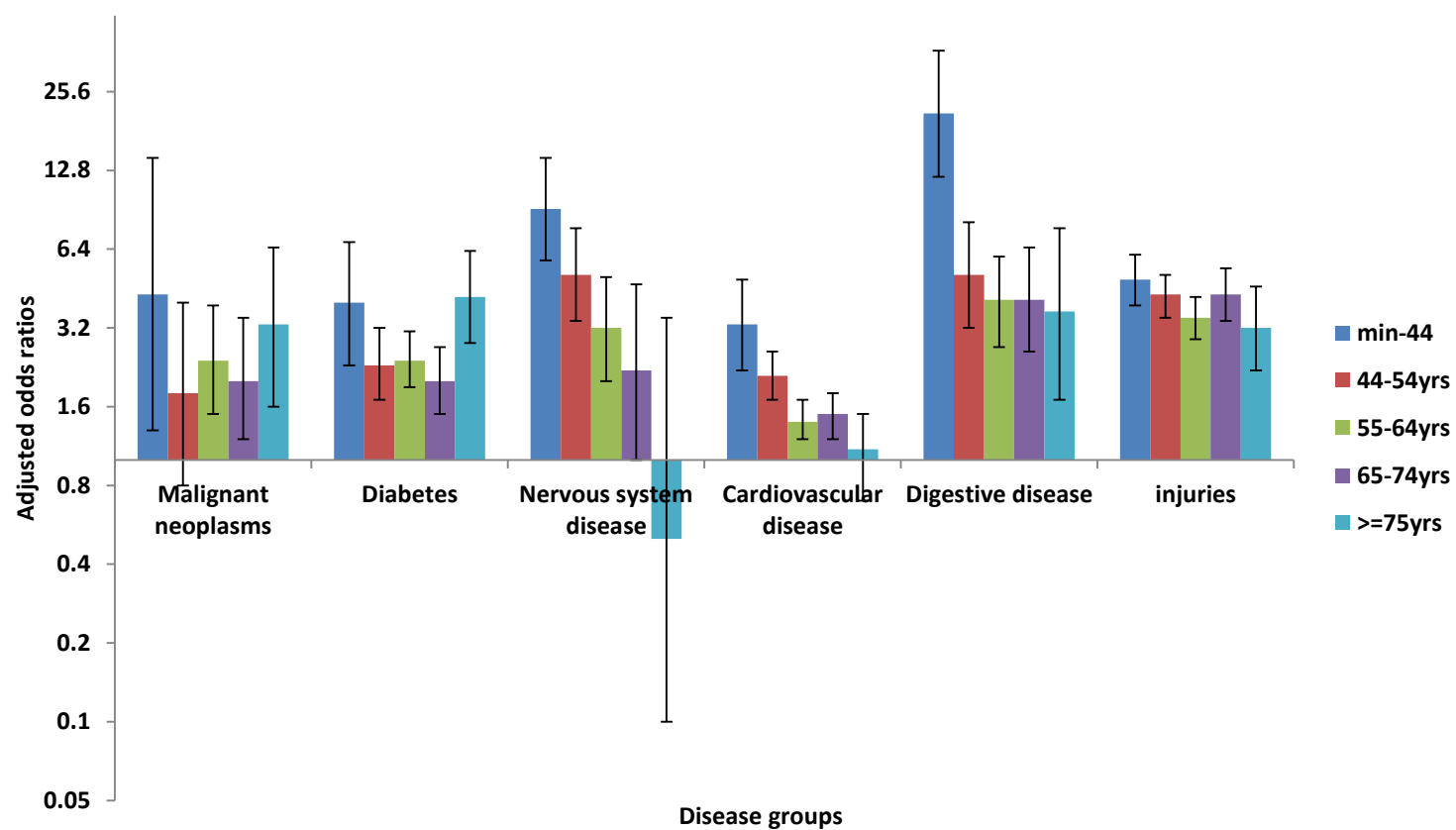


Figure 5-1 Adjusted odds ratios for each alcohol-attributable disease, stratified by age

Table 5-5 shows proportions and odds ratios computed for each condition within each of the six ICD categories. Due to small numbers the different injuries assessed were simply grouped into intentional or unintentional injuries (intentional injuries also included injuries of undetermined intent).

Assessing proportions within each ICD 10 category (Table 5-5), showed that within each category, certain conditions were more strongly associated with subsequent diagnosis of alcoholic cirrhosis than others. For example, within the cardiovascular disease category, cardiac arrhythmias had the strongest association with alcoholic cirrhosis (Adjusted OR 4.2, 95% CI [3.3-5.6]) compared to hypertension (adjusted OR 1.5, 95% CI [1.3-1.7]) or cerebrovascular diseases (adjusted OR 1.8, 95% CI [1.4-2.3]). Among injuries, intentional injuries and self-harm (Adjusted OR 6.6, 95% CI [5.4-7.9]) were more strongly associated with subsequent diagnosis with alcoholic cirrhosis than unintentional injuries (OR 3.7, 95% CI [3.4-4.1]).

Table 5-5 Proportions and ORs for all morbidities for cases and controls

Conditions	Cases (n=2479)	Controls (n=24,790)	OR (95% CI)	
			Unadjusted	Adjusted'
Malignant neoplasms of:				
Larynx	5(0.2)	6(0.02)	8.3(2.5-27.4)	6.8(1.9-23.5)
Colon and rectum	11(0.4)	82(0.3)	1.3(0.7-2.5)	1.3(0.7-2.5)
Breast	12(0.48)	212(0.9)	0.6(0.3-1.0)	0.9(0.5-1.6)
Oesophagus	4(0.2)	12(0.1)	3.3(1.1 -10.4)	3.5(1.1-11.3)
Lip, oral cavity and pharynx	7(0.3)	18(0.1)	3.9(1.6-9.3)	2.6(1.0-6.4)
Diabetes^	318(12.8)	1,303(5.3)	2.6(2.3-3.0)	2.6(2.2-2.9)
Diseases of the nervous system				
Epilepsy	125(5.0)	264(1.1)	4.9(3.9-6.1)	4.4(3.5-5.5)
Cardiovascular diseases				
Cardiac arrhythmias	84(3.4)	220(0.9)	3.9(3.0-5.1)	4.2(3.3-5.6)
Cerebrovascular diseases	96(3.8)	468(1.9)	2.1(1.7-2.6)	1.8(1.4-2.3)
Hypertensive diseases	359(14.5)	2,605(10.5)	1.4(1.3-1.6)	1.5(1.3-1.7)
Ischaemic heart disease	160(6.5)	1,161(4.6)	1.4(1.2-1.7)	1.2(0.9-1.4)
Digestive diseases				
Pancreatitis	83(3.4)	49(0.2)	17.5(12.2-25.0)	15.4(10.6-22.5)
Cholelithiasis	81(3.3)	271(1.1)	3.1(2.4-3.9)	3.1(2.4-4.1)
Injuries				
Unintentional injuries*	790 (31.8)	2,753 (11.1)	3.7(3.4-4.1)	3.7(3.4-4.1)
Intentional injury/self-harm+	236 (9.5)	319 (1.3)	8.1 (6.8-9.6)	6.6(5.4-7.9)

*Unintentional injuries include falls, fractures, asphyxia, road traffic accidents and unintentional poisonings.

+Intentional injuries include assault, intentional self-harm, intentional poisoning and injuries of undetermined intent

^excludes gestational diabetes 'adjustment for age, sex and smoking status

Table 5-6 and Figure 5-2 shows proportions and ORs for assessed conditions at different time periods. There were variations in the odds of the various conditions over time with some conditions increasing and others decreasing (Table 5-6 and Figure 5-2). Digestive diseases and diabetes were more likely to occur around cirrhosis diagnosis than at other times; adjusted ORs for digestive diseases were 11.9 (95% CI [8.3-17.2]) in the 0-12 month period and 1.7 (95% CI [0.8-4.0]) in the 6-10 year period and the adjusted ORs for diabetes were 3.9 (95% CI, [2.9-5.1]) in the 0-12 month period and 1.7 (95% CI, [1.1-2.6]) in the 6-10 year period. ORs for cardiovascular diseases did not change markedly throughout the entire 10 year window but were slightly higher in the 6-10 year period than in earlier periods. Epilepsy and intentional injuries had relatively high ORs which persisted strongly throughout the entire 10 year period assessed.

Table 5-6 The proportion of patients presenting with each examined condition at different periods before cirrhosis diagnosis with OR (95% CI) comparing cases to controls.

Time to diagnosis	At risk n (%)	cases	At risk controls n (%)	OR (95% CI)	
				Unadjusted	Adjusted'
Malignant neoplasms					
0-12months	38 (1.5)		83 (0.3)	4.6(3.1-6.8)	5.1(3.4-7.8)
13mths- 2yrs	9(0.4)		61(0.3)	1.4(0.7-2.8)	1.9(0.9-3.9)
3-5yrs	11(0.8)		68(0.6)	1.3(0.7-2.5)	1.6(0.8-3.1)
6-10yrs	-		40(1.2)	-	-
Diabetes					
0-12months	78 (3.2)		207 (0.8)	3.8(2.9-5.0)	3.9(2.9-5.1)
13mths- 2yrs	52 (2.4)		183(0.9)	2.7(1.9-3.7)	2.3(1.7-3.2)
3-5yrs	61(4.4)		228(2.0)	2.2(1.7-3.0)	2.1(1.5-2.8)
6-10yrs	28(5.9)		109(3.2)	1.9(1.2-2.9)	1.7(1.1-2.6)
Nervous system diseases					
0-12months	38(1.5)		39(0.2)	9.9(6.3-15.5)	9.7(6.0-15.7)
13mths- 2yrs	13(0.6)		35(0.2)	3.5(1.8-6.6)	2.4(1.2-4.6)
3-5yrs	13(0.9)		42(0.4)	2.6(1.4-4.8)	2.4(1.2-4.6)
6-10yrs	18(3.7)		22(0.6)	6.0(3.2-11.3)	5.6(2.8-11.0)
Cardiovascular diseases					
0-12months	96(3.9)		681(2.8)	1.4(1.1-1.8)	1.4(1.1-1.7)
13mths- 2yrs	71(3.3)		559(2.8)	1.2(0.9-1.5)	1.1(0.8-1.4)
3-5yrs	125(9.1)		827(7.2)	1.3(1.1-1.5)	1.2(0.9-1.5)
6-10yrs	71(14.7)		337(9.8)	1.6(1.2-2.1)	1.4(1.1-1.9)
Digestive diseases					
0-12months	68(2.7)		63(0.3)	11.1(7.8-15.7)	11.9(8.3-17.2)
13mths- 2yrs	21(0.9)		49(0.2)	4.0(2.4-6.8)	3.3(1.9-5.7)
3-5yrs	23(1.7)		67(0.6)	2.9(1.8-4.6)	2.9(1.8-4.9)
6-10yrs	8(1.7)		29(0.8)	1.9(0.9-4.3)	1.7(0.8-4.0)
Unintentional injuries					
0-12months	198(7.9)		525(2.1)	4.0(3.4-4.8)	3.9(3.2-4.6)
13mths- 2yrs	124 (5.8)		418(2.1)	2.9(2.4-3.5)	2.7(2.2-3.3)
3-5yrs	148(10.7)		701(6.1)	1.8(1.5-2.2)	1.8(1.5-2.2)
6-10yrs	94(19.5)		297(8.7)	2.5(1.9-3.3)	2.6(2.0-3.4)
Intentional injury/self-harm					
0-12months	29(1.2)		73(0.3)	4.0(2.6-6.2)	3.0(1.9-4.7)
13mths- 2yrs	40(1.9)		53(0.3)	7.2(4.8-10.9)	5.9(3.8-9.0)
3-5yrs	50(3.6)		55(0.5)	7.8(5.3-11.5)	6.3(4.2-9.6)
6-10yrs	32(6.6)		32(0.9)	7.6(4.6-12.5)	6.8(3.9-11.7)
Numbers at risk within each analyses time period					
0-12months	2,479 (100.0)		24,790 (100.0)		
13months-2years	2,151 (86.8)		20,162 (81.3)		
3-5years	1,377(55.6)		11,422(46.1)		
6-10years	482 (19.4)		3,432(13.8)		

^a Adjustment for age, sex and smoking status - number within cell <5

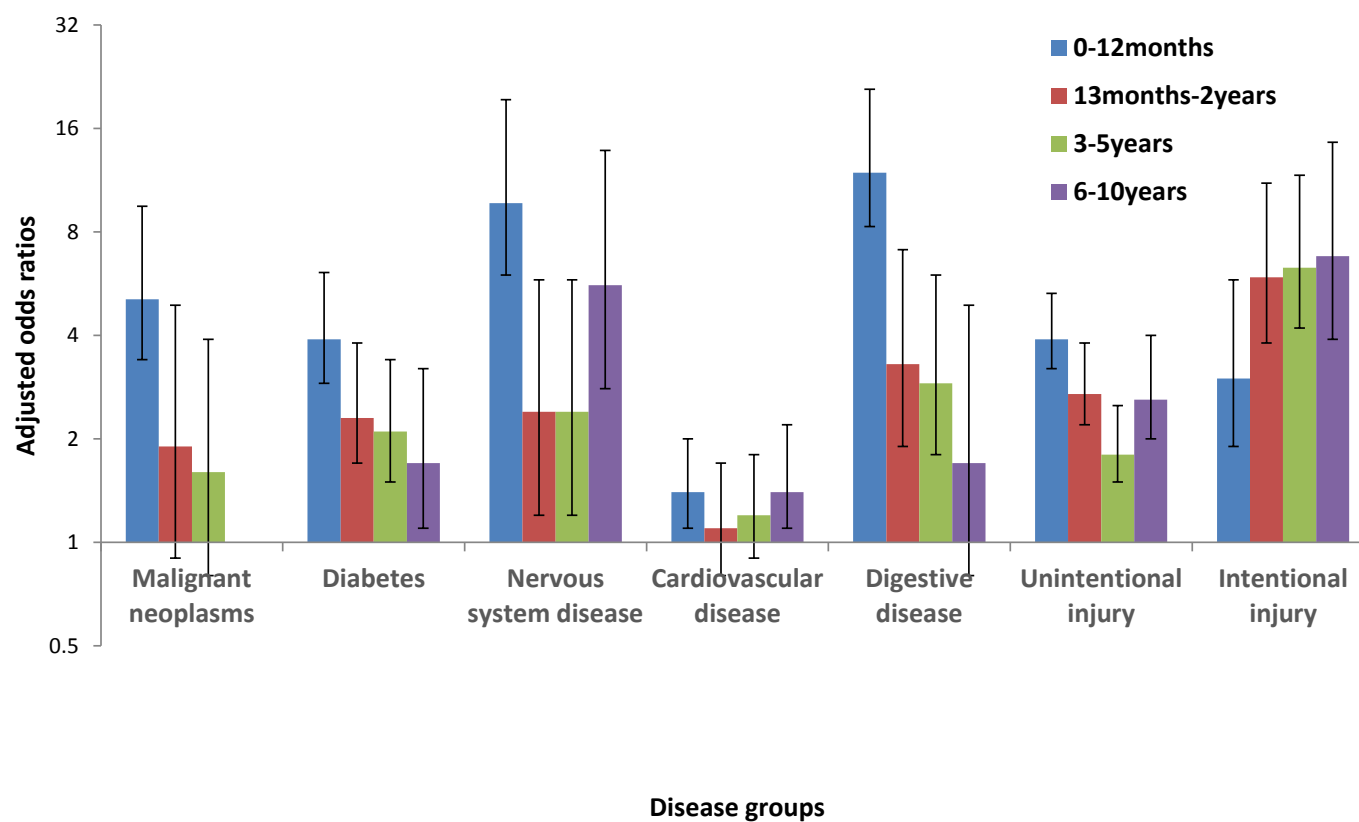


Figure 5-2 Adjusted Odds ratios for each alcohol-attributable morbidity, stratified by time to diagnosis

5.4 Discussion and Interpretation

5.4.1 Main findings

This study has shown that, compared with patients in the general population, those patients who acquire a diagnosis of alcoholic cirrhosis present more frequently with other conditions reported to be attributable to alcohol, specifically injuries (intentional and unintentional), cardiovascular diseases, diabetes, digestive diseases and epileptic seizures, and that this excess disease burden is present as far back as 10 years before the diagnosis of alcoholic cirrhosis. These findings imply for the first time that it could be possible to identify people who are at risk of alcoholic cirrhosis through health care attendances in either primary or secondary care for other conditions partially attributable to alcohol.

The conditions with the highest frequency of consultation in cases were injuries (unintentional), cardiovascular diseases (hypertension in particular), and diabetes. However, these did not appear to be particularly specific to alcoholic cirrhosis as they were also reasonably prevalent among the control population. Digestive diseases, intentional injuries and epilepsy which were relatively uncommon among cases, appeared to be more strongly associated with alcoholic cirrhosis. It could therefore be argued that while targeting individuals with any alcohol-attributable disease may be beneficial, focussing on those who present with any of these three conditions (digestive diseases, intentional injuries and epilepsy) may be a more sensitive way of identifying people who will be more likely to develop alcoholic cirrhosis of the liver later on. Finally, the magnitude of risks for all morbidities varied by age, and risks were typically highest among those under 45 years of age.

5.4.2 Study strengths and limitations

Most of the strengths of this study lie with the data and methodological techniques and, as discussed already in the previous chapter, these include the large number of patients, the population-based design, the representativeness of the CPRD and HES data and the age and GP practice matched comparator group.

In addition to these general strengths, there are a number of study specific strengths. First, because the morbidities assessed were prospectively recorded in routinely collected data before the diagnosis of alcoholic cirrhosis rather than being recalled retrospectively by patients, information bias due to recall has been avoided. Another important strength is the fact that the alcohol-attributable conditions were looked at in more detail than in previous studies; by assessing age and time before diagnosis interactions a more comprehensive description of comorbidities was provided.

Nonetheless, there are some limitations to this study. Although age differences in healthcare seeking behaviour have been accounted for through frequency matching, there was no data on other potential modifiers of this e.g. socio-economic status, education and family history and therefore these have not been adjusted for. It is therefore not possible to rule out the likelihood that residual confounding has an effect on the study estimates. Intentionally, the study estimates have not been adjusted for level of alcohol use since alcohol consumption is directly on the causal pathway of alcoholic cirrhosis and thus adjustment would be inappropriate.

The partly alcohol-attributable morbidities assessed were prospectively recorded in the medical record before the diagnosis of alcoholic cirrhosis. However there is still the possibility of reverse causality bias, particularly in the association between diabetes and cirrhosis that was observed. Several studies have shown that metabolic syndrome related to pre-existing diabetes may result in an increased predisposition to cirrhosis(197–199). Alternatively, it has also been implied that impaired glucose

metabolism in cirrhosis can lead to diabetes(200–202). Since, as with all epidemiological studies of chronic diseases with long subclinical periods (i.e. both diabetes and cirrhosis), it is only possible to identify the date of acquisition of cirrhosis (or diabetes) diagnosis rather than the date of biological onset, it becomes difficult to definitively establish the temporal association of the relationship.

The exceptionally high risk of digestive diseases and diabetes that was found within the year of cirrhosis diagnosis compared to other later periods may reflect another potential problem, namely ascertainment bias.

This may occur during gastro-intestinal based work-up for cirrhosis diagnosis where clinical suspicion of liver disease was high in the year prior to diagnosis of alcoholic cirrhosis. However, it could also be argued that perhaps the presence of other digestive diseases may have led to quicker diagnosis of alcoholic cirrhosis, since those with these morbidities would have been more likely to utilise healthcare services particularly gastroenterology and hepatology services which are likely to think more about cirrhosis leading to increased opportunities to identify cirrhosis.

Finally, the results have shown a higher risk of several malignancies (oropharynx, oesophageal and laryngeal cancers) among people with alcoholic cirrhosis. A common factor that is also strongly associated with these malignancies is cigarette smoking (203–205). Since nearly half of the cases included in our study were identified as smokers, it is likely that the higher risk of laryngeal and oesophageal cancer found in this thesis may well be related more importantly to smoking and only partly to alcohol. Though adjustments were made for the most recent documented smoking status this is probably an imperfect measurement of true lifetime smoking habit (e.g. adjustment for pack-years was not possible as this level of detail is not available in the thesis data) and

there will likely be residual confounding by smoking in operation in the adjusted effect estimates.

5.4.3 Comparison with previous literature

There are limited studies published on healthcare use and morbidities in people with alcoholic cirrhosis with which the results of the study can be compared to. As noted earlier, Verrill et al (2006) retrospectively reviewed hospitalised patients with alcoholic cirrhosis in Southampton, UK between 1995 and 2000 to identify how often patients had made contact with primary or secondary care in the five year period before they received a diagnosis of alcoholic cirrhosis(80). Similar to the findings reported here, they report that patients had presented with injuries, seizures, oral cancers and digestive diseases during the period before alcoholic cirrhosis was diagnosed(80). Though representative of the population served by this hospital, these findings are unlikely to be generalizable to the rest of the UK population with alcoholic cirrhosis. More so, due to the absence of any control population, it is difficult to make direct comparisons between this previous study and the reported study. In another study in Scotland UK where high healthcare utilisation of patients with alcohol use disorders including alcoholic liver disease has been shown, morbidities that patients presented with before the disease were not reported(81).

5.4.4 Conclusion and implications

The partly alcohol-attributable conditions that patients consult for in either primary or secondary care may be useful as an indication of potential development of alcoholic cirrhosis. Practitioners could therefore combine the early warning signs that diagnosis of these partially alcohol-attributable diseases and injuries imply with other important prognostic information to increase their assessment of alcohol misuse in individuals.

By identifying those at risk of alcohol related harm individuals can be motivated to cut down their drinking to safer levels before significant harms are established (108). Particular attention should also be paid to those diagnosed with more than one partially alcohol attributable morbidity as the likelihood of a subsequent diagnosis of alcoholic cirrhosis was 9-fold higher for patients with three or more of these identified morbidities. From a practical perspective, these diagnoses might be separated in time and may not be identified quickly in the practice setting. Therefore in order to capture those at risk, the information provided in this study could be extended to develop an automatic risk predictive scoring tool that would alert practitioners to patients that have a history of any these conditions. Similar tools have been developed for use in identifying people at risk of other chronic diseases such as epilepsy, cancers and several cardiovascular diseases.

The stronger associations found between all diseases and cirrhosis for those less than 45 years of age suggests that the potential advantage of risk stratification using alcohol-attributable health care attendances may be even greater in this age group.

In conclusion, this study has shown that among most of the patients diagnosed with alcoholic cirrhosis, prior primary or secondary care diagnoses for conditions known to be attributable to alcohol are common and are more common than in the general population. These findings suggest that practitioners may be able to identify those who may later develop alcoholic cirrhosis of the liver by reviewing people presenting with partially alcohol-attributable conditions more closely. If these high risk groups of patients can be identified and screened for alcohol misuse, and treated appropriately, practitioners may be able to help reduce or avoid the long term consequences of development of alcoholic liver disease.

ALCOHOLIC PSYCHOSIS

Chapter 6

6 Healthcare utilisation and recording of alcohol status and interventions in men and women prior to alcoholic psychosis

As previously described, alcoholic psychosis is one of the important manifestations of chronic alcoholism. It is a relatively rare disease but is associated with a serious health risk including an increased risk of suicide, depression and rehospitalisation with no available evidence based treatment.

Due to above consequences one would expect alcoholic psychosis to be associated with high use of healthcare, not only at the time of diagnosis but also prior to it, thereby providing opportunities for the earlier identification and treatment of high risk patients. But this has not yet been investigated and indeed, generally, alcoholic psychosis has been understudied in the research world.

The aim of this study was to therefore assess whether patients with alcoholic psychosis made regular use of healthcare services prior to the disease diagnosis in comparison to the control population. Additionally, as a step towards improving disease prevention the extent to which patients were screened for alcohol use, and the extent to which those identified as consuming alcohol at high risk were offered any alcohol related interventions was assessed.

6.1 Methods

6.1.1 Study population

Cases of alcoholic psychosis were those patients identified using definition 1 as described in chapter 3. From the remaining CPRD-HES linked patients without a history

of psychosis 10 control patients were selected for each case of alcoholic psychosis frequency matched by age ($\pm$ 5 years) and general practice.

A date of diagnosis, defined as the date for the first record of alcoholic psychosis, was assigned to cases. Controls were assigned a “pseudo-diagnosis” date which was a randomly generated date between 1 year after the start of the linked dataset (1997) up to the date they left the practice or died.

6.1.2 Observation period

The study start date for each patient was the latest of (i) the start of the linked dataset (1st April 1997), (ii) the date a patient registered with a GP practice, or (iii) the date when the practice attained an acceptable level of data recording, whichever came first. The study end date was the date of alcoholic psychosis diagnosis/ pseudo-diagnosis.

6.1.3 Outcomes

The main outcome measures were primary and secondary health care utilisation and the extent of alcohol use or brief intervention delivery recording for each patient prior to alcoholic psychosis diagnosis/pseudo-diagnosis. The methods for quantifying these outcomes are as per in the cirrhosis work and as previously described in section 3.3.

Briefly, to quantify healthcare utilisation, all clinical consultation events in which there was a direct face-to-face contact between a GP and a patient were extracted from patients CPRD files. Similarly, all patient hospital admission events prior to diagnosis of psychosis were extracted from HES.

Alcohol use status as well as information on whether a patient had ever received any alcohol intervention was defined using methods described in section 3.3.3.

For each patient, information on age (categorised as 18-44, 45-54, 55-64, 65-74, and $\geq$ 75 years) and sex were extracted as potential confounders from CPRD.

6.1.4 Statistical analysis

Descriptive statistics for all baseline parameters of the study population was calculated.

The proportion of patients with alcohol use records or records of an offer of an intervention was calculated and odds ratios comparing cases to controls were estimated using logistic regression. Potential confounding variables explored in the logistic regression model were age and patient consulting rate; a potential confounding variable was retained in the model only if it altered the unadjusted odds ratio by more than 10%.

To examine if the likelihood of having an alcohol use record or the record of an intervention varied by sex or across age-groups, interaction tests were carried out by fitting interaction terms in the logistic regression models for each outcome separately and conducting a likelihood ratio test at a significance level of $p < 0.05$.

With regard to healthcare utilisation, overall and yearly rates of primary care consultations and hospital admissions were estimated for cases and controls. Overall rates were calculated using the total number of consultations (or admissions) made by each group (cases or controls) during the study period as the numerator, and the total person years they contributed as the denominator. Yearly rates were calculated using the total number of consultations (or admissions) assigned to each year before index date for each group as the numerator and the total person years at risk in each year as the denominator. Excess healthcare use in cases was estimated by calculating the absolute difference between rates in cases and the corresponding control population. Rate ratios for cases in comparison to controls with 95%-confidence intervals (95% CIs) were estimated using Poisson regression model applying cluster robust variance estimation to account for homogeneity within practices. Interaction between age or sex and consulting/admission rates was assessed by fitting an interaction term

between them in the Poisson model and conducting a likelihood ratio test at the 5% level of significance.

6.2 Results

6.2.1 Study population characteristics

A total of 1,731 cases of alcoholic psychosis and 17,310 controls were included in the analysis. The median observation time prior to diagnosis /pseudo-diagnosis was 5.5 years for cases and 4.4 years for the control group. The mean age at alcoholic psychosis diagnosis was 52.9 years. Cases of psychosis were more likely to be males than females (Table 6-1).

Table 6-1 Baseline demographics of cases of alcoholic psychosis and controls matched by age and GP practice

	Cases (n=1,731)	Controls (n =17,310)	P value ¹
Age at diagnosis(years)			
Mean(SD)	53.3(17.4)	53.3(17.5)	0.55*
Age group (n, %)			
18-44	595(34.4)	5,999(34.7)	0.79
45-54	334(19.3)	3,375(19.5)	
55-64	335(19.4)	3,170(18.3)	
65-74	236(13.6)	2,325(13.4)	
≥ 75	231(13.3)	2,441(14.1)	
Observation time(years)			
Median(IQR)	5.5(2.6-9.2)	4.4(2.3-8.2)	
Sex (n, %)			
Male	1,156(66.8)	8,481(49.0)	<0.001
Female	575(33.2)	8,829(51.1)	

¹Chi squared tests p value unless indicated otherwise
*ttest p value

6.2.2 Use of primary healthcare prior to the diagnosis of alcoholic psychosis

As shown in Table 6-2, the overall rate of primary care consultation among alcoholic psychosis patients was approximately 10 consultations per year compared to 7 consultations per year in the control population. This corresponds to a 53% higher consultation rate [Rate ratio 1.53, CI 1.52 to 1.54] or an average excess of 3 more consultations per year compared to the control population. The greatest excesses in primary care use were found in the years closest to diagnosis (Figure 6-1). Patients with psychosis had an average excess of between 3 to 7 consultations in the 5 years immediately before diagnosis compared to an excess of between 1 to 2 consultations at 6 to 10 years before diagnosis. The absolute rate of consultations was higher in women than men; however, comparing cases to controls men had significantly greater excesses than women (p value for likelihood ratio test for sex interaction < 0.0001).

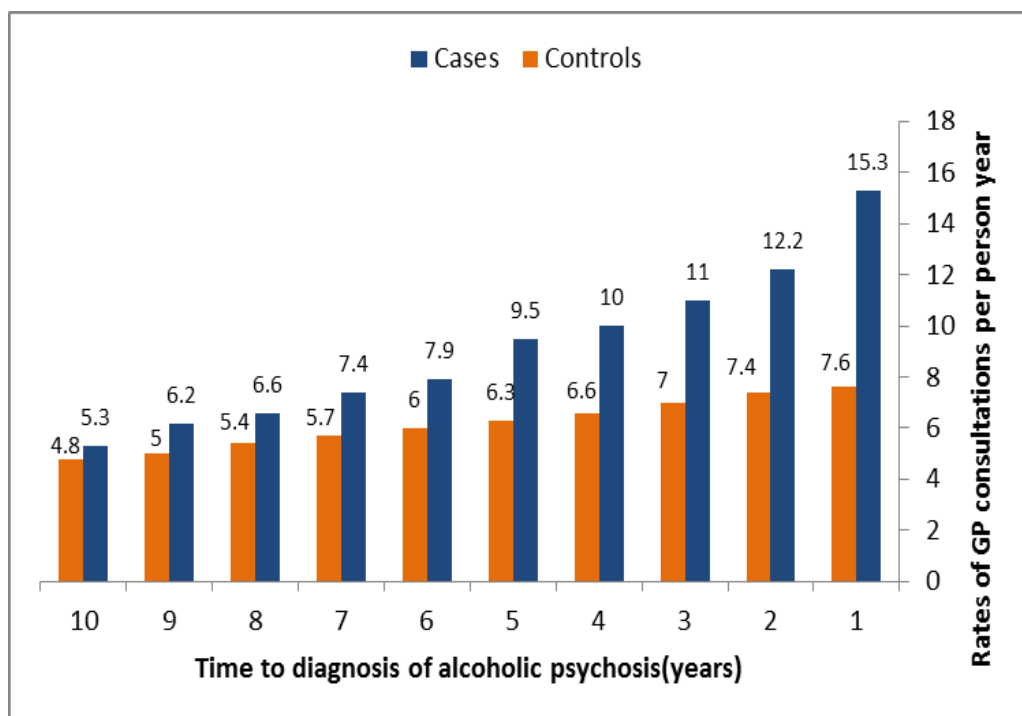
Table 6-2 Overall and yearly primary care consultation rates and rate ratios of cases of alcoholic psychosis and controls

	Overall				Males				Females			
	Rate per person-years				Rate per person-years				Rate per person-years			
	Cases	Controls	Excess	IRR(95% CI)	Cases	Controls	Excess	IRR(95% CI)	Cases	Controls	Excess	IRR(95% CI)
Overall study period	9.9	6.5	3.4	1.53(1.52-1.54)	9.1	5.2	3.9	1.76(1.74-1.78)	11.5	7.7	3.8	1.49(1.48-1.51)
Time to diagnosis(yrs.)												
1	15.3	7.6	7.7	2.02(1.99-2.04)	14.4	6.1	8.3	2.35(2.31-2.39)	17.0	9.0	8.0	1.90(1.86-1.94)
2	12.2	7.4	4.8	1.65(1.63-1.68)	11.2	6.0	5.2	1.86(1.82-1.89)	14.2	8.7	5.5	1.63(1.59-1.67)
3	11.0	7.0	4.0	1.57(1.55-1.6)	10.1	5.7	4.4	1.77(1.73-1.81)	12.9	8.3	4.6	1.56(1.52-1.6)
4	10.0	6.6	3.4	1.51(1.48-1.54)	9.2	5.3	3.9	1.74(1.69-1.78)	11.7	7.9	3.8	1.47(1.43-1.52)
5	9.5	6.3	3.2	1.49(1.46-1.52)	8.7	5.0	3.7	1.73(1.68-1.78)	11.0	7.6	3.4	1.44(1.39-1.49)
6	7.9	6.0	1.9	1.31(1.27-1.34)	6.8	4.8	2.0	1.43(1.38-1.48)	10.1	7.2	2.9	1.39(1.34-1.45)
7	7.4	5.7	1.7	1.31(1.27-1.35)	6.7	4.5	2.2	1.5(1.44-1.56)	8.9	6.8	2.1	1.3(1.25-1.36)
8	6.6	5.4	1.2	1.22(1.18-1.26)	6.1	4.2	1.9	1.45(1.39-1.51)	7.7	6.6	1.1	1.17(1.11-1.23)
9	6.2	5.0	1.2	1.23(1.19-1.28)	5.6	3.8	1.8	1.47(1.40-1.55)	7.4	6.2	1.2	1.2(1.13-1.27)
10	5.3	4.8	0.5	1.11(1.06-1.16)	4.8	3.6	1.2	1.37(1.29-1.45)	6.3	5.9	0.4	1.06(0.99-1.14)

Likelihood ratio test p value for the interaction between sex and consultation rates, with adjustment for age: <0.0001

Note: Due to the small number of patients contributing data more than 10 years before diagnosis, yearly consultation rates, rate ratios and rate differences were only estimated for the 10 year period prior to diagnosis/pseudo-diagnosis.

Figure 6-1 Yearly primary care consultation rates per person-year prior to
alcoholic psychosis



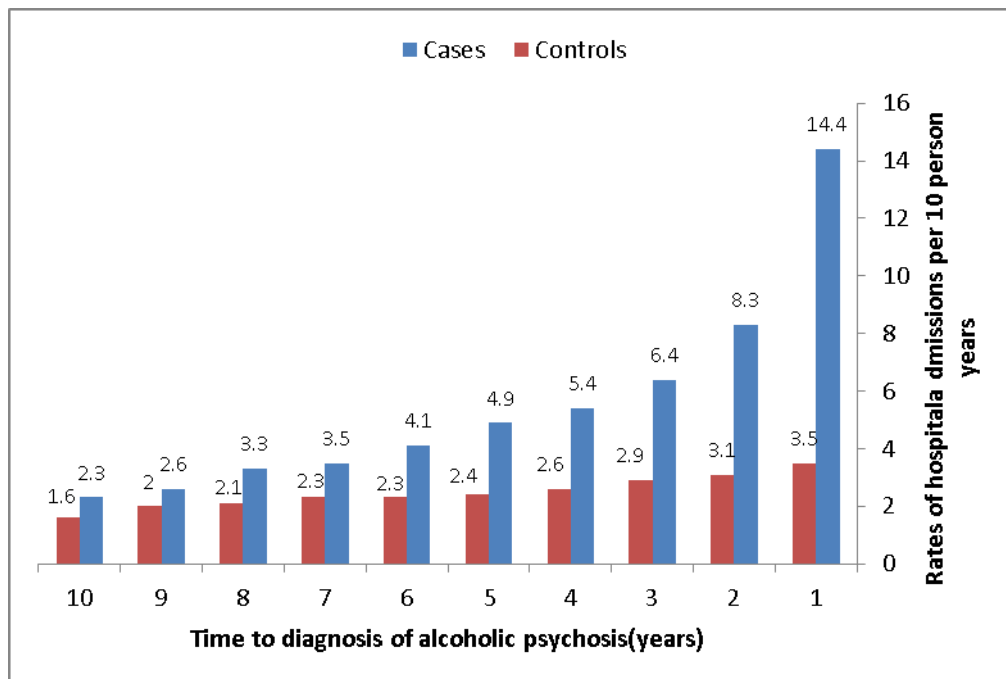
6.2.3 Use of hospital services

Across the entire study period, 77% of cases were previously hospitalized before psychosis diagnosis compared to 41% of the control group. Rates of hospital admissions were over twice as high for patients with alcoholic psychosis than for the control population (Table 6-3). Admissions were particularly more frequent in the years close to diagnosis and there was a 4 fold increase in admission rates in patients than controls in the year of diagnosis (Figure 6-2). Tests for sex interaction with admission rates were borderline significant (likelihood ratio test for interaction between sex and rates of admission $p=0.04$). Men appeared to have a slightly higher number of excess admissions than women, but only particularly within the three years before diagnosis. In subsequent years, women had higher excesses of admissions than men.

Table 6-3 Overall and yearly admission rates and rate ratios of cases of alcoholic psychosis and controls

Overall				Males				Females				
Rate per 10 person-years				Rate per 10 person-years				Rate per 10 person-years				
Cases	Controls	Excess	IRR(95% CI)	Cases	Controls	Excess	IRR(95% CI)	Cases	Controls	Excess	IRR(95% CI)	
Overall study period												
6.3	2.7	3.6	2.4(2.3-2.5)	6.4	2.6	3.8	2.5(2.4-2.6)	6.5	2.8	3.7	2.4(2.3-2.5)	
Time to diagnosis(yrs.)												
1	14.4	3.5	10.9	4.1(3.9-4.3)	14.7	3.3	11.4	4.5(4.2-4.8)	13.9	3.8	10.1	3.7(3.4-4)
2	8.3	3.1	5.2	2.7(2.5-2.8)	8.5	2.9	5.6	2.9(2.7-3.2)	7.8	3.3	4.5	2.4(2.1-2.6)
3	6.4	2.9	3.5	2.2(2.0-2.3)	6.5	2.8	3.7	2.3(2.1-2.5)	6.1	3.1	3	2.0(1.8-2.3)
4	5.4	2.6	2.8	2.1(1.9-2.2)	5.4	2.7	2.7	2.0(1.8-2.3)	5.4	2.6	2.8	2.1(1.8-2.4)
5	4.9	2.4	2.5	2(1.8-2.2.0)	4.9	2.5	2.4	2.0(1.7-2.2)	5.0	2.4	2.6	2.1(1.8-2.4)
6	4.1	2.3	1.8	1.8(1.6-2.0)	3.6	2.4	1.2	1.5(1.3-1.7)	5.0	2.2	2.8	2.3(1.9-2.7)
7	3.5	2.3	1.2	1.5(1.3-1.7)	2.8	2.6	0.2	1.1(0.9-1.3)	4.8	2.1	2.7	2.3(1.9-2.8)
8	3.3	2.1	1.2	1.6(1.3-1.8)	2.6	2.3	0.3	1.1(0.9-1.4)	4.8	1.9	2.9	2.5(2-3.1)
9	2.6	2.0	0.6	1.3(1.1-1.6)	2.5	1.9	0.6	1.3(1.0-1.6)	2.8	2.0	0.8	1.4(1-1.9)
10	2.3	1.6	0.7	1.4(1.1-1.7)	2.3	1.6	0.7	1.5(1.1-1.9)	2.2	1.7	0.5	1.3(0.9-1.9)
Likelihood ratio test p value for the interaction between sex and admission rates with adjustment for age: 0.04												

Figure 6-2 Yearly hospital admission rates per 10 person-years prior to alcoholic psychosis diagnosis.



6.2.4 Alcohol use screening/recording

A total of 1,369(79.1%) cases and 11,326(65.4%) of controls had an alcohol use status recorded within their medical records (Table 6-4). Of the cases, 52% had the earliest alcohol status record more than 5 years before alcoholic psychosis diagnosis, 27% had theirs between 2 and 5 years pre-diagnosis while for 9% it was during the year before they were diagnosed (Table 6-5).

Substantially more cases than controls had a record of harmful or hazardous drinking (50.8% vs 8.6%). Of the cases, 43% had this record of problem drinking 5 or more years before alcoholic psychosis was diagnosed, 28% had theirs between 2 to 5 years pre-diagnosis while the remaining 16% had theirs in the year of psychosis diagnosis (Table 6-6). Across the entire case population, the mean time between recognition of harmful drinking and alcoholic psychosis diagnosis was 4.0 years.

Table 6-4 Proportion of patients with any record of alcohol use

	Cases n=1,731 (n, %)	Controls n=17,310 (n, %)	P value ¹
Any record of alcohol use	1,369(79.1)	11,326(65.4)	<0.001
Never	54(3.1)	1,871(10.8)	
Moderate	298(17.2)	7,316(42.3)	
Hazardous/harmful	881(50.8)	1,496(8.6)	
Unclear	136(7.9)	643(3.7)	
Data not recorded	362(20.9)	5,984(34.6)	
¹ chi squared test p value			

Table 6-5 Time between earliest alcohol use record and diagnosis of alcoholic psychosis or pseudo-diagnosis among those with a record of alcohol use

	Cases n=1,369 (%)	Control group n=11,326 (%)
Time to diagnosis or pseudo-diagnosis (years)		
=<1year	119 (8.7)	656 (5.8)
>1-2years	169 (12.3)	1,774 (15.7)
>2-5years	373 (27.3)	3,399 (30.0)
>5years	708 (51.7)	5,501 (48.6)

Table 6-6 Timing between harmful or hazardous drinking record and alcoholic psychosis diagnosis/pseudo-diagnosis among those with a record of harmful or hazardous drinking

	Cases n=881 (%)	Control group n=1,496 (%)
Time to diagnosis/pseudo-diagnosis in years		
=<1year	141 (16.0)	152 (10.2)
>1-2years	120 (13.6)	225 (15.0)
>2-5years	246 (27.9)	442 (29.6)
>5years	374 (42.5)	677 (45.3)

Table 6-7 shows the prevalence of alcohol use records stratified by sex and age.

There was a significant interaction between the recording of alcohol use and sex (likelihood ratio test p value for sex interaction= 0.0012). Compared to the control population, men with alcoholic psychosis appeared to be more likely than women to have any alcohol use record [men adjusted OR 1.7, 95% CI 1.5-2.0; women adjusted OR 1.2, 95% CI 0.9-1.5].

When records were assessed by age-groups, there was no significant difference in the prevalence of records across age groups. The likelihood ratio test for age interaction was 0.12 (Table 6-7). However, stratifying results by age yet highlighted the higher likelihood of men to have an alcohol use record compared to women.

Table 6-7 Proportion of patients with any alcohol use record stratified by sex and age and OR and 95% Cis

	Overall			Males			Females		
	Cases	Controls	OR(95% CI)	Cases	Controls	OR(95% CI)	Cases	Controls	OR(95% CI)
	N=1,731	N=17,310		n=1,156	n=8,481		n= 575	n=8,829	
Overall	1,369(79.1)	11,326(65.4)	1.5(1.3-1.7) ^a	928(80.3)	5,307(62.6)	1.7(1.5-2.0) ^b	441(76.7)	6,019(68.2)	1.2(0.9-1.5) ^b
Age at diagnosis (years)									
18-44	437(73.4)	3718(61.9)	1.8(1.5-2.3)	307(74.3)	1704(55.9)	2.3(1.8-2.8)	130(71.4)	2014(68.3)	1.2(0.9-1.7)
45-54	274(82.0)	2239(66.3)	2.5(1.9-3.3)	181(81.9)	1112(64.1)	2.6(1.9-3.6)	93(82.3)	1127(68.8)	2.1(1.4-3.4)
55-64	287(85.7)	2137(67.4)	2.9(2.2-4.2)	206(86.2)	1051(65.6)	3.5(2.3-5.2)	81(84.3)	1086(69.3)	2.3(1.2-4.2)
65-74	188(79.7)	1608(69.2)	1.7(1.2-2.5)	125(83.3)	768(67.5)	2.2(1.4-3.5)	63(73.3)	840(70.8)	1.2(0.7-2.1)
≥ 75	183(79.2)	1624(66.5)	1.9(1.3-2.7)	109(82.0)	672(70.4)	2.1(1.3-3.4)	74(75.5)	952(64.0)	1.6(1.0-2.7)
^a OR adjusted for age, sex and consulting rate of patients ^b OR adjusted for age and consulting rate of patients LRT for interaction between sex and alcohol use: 0.0012 LRT for age interaction: significant 0.12									

6.2.5 Records of alcohol intervention

Of the entire case population, 19.6 % (n=340) had records showing that they had been previously given a brief alcohol intervention or a referral to a specialist alcohol treatment Centre (Table 6-8). The most commonly recorded intervention was “brief advice” or “extended advice”; 314 patients of the 340 identified with interventions had records of brief or extended advice.

When intervention records were stratified by sex, there was no difference in the prevalence of interventions between men and women (likelihood ratio test p value for sex interaction = 0.05). However across age groups, significant differences were identified (likelihood ratio test p value for age interaction= 0.02). Patients aged 18-44 years [OR 4.3 95%CI 3.1-5.8] were more likely to have interventions compared to those who were older [OR for 45-54 years 3.2, 95% CI 2.2-4.8; OR for ≥ 75 years 2.4, 95% CI 1.5-3.7] (Table 6-9).

Table 6-8 Proportion of patients with any record of brief alcohol intervention and alcohol related referral

	Cases n=1,731	Controls n=17,310	
Intervention			
Documented offer of an intervention	340(19.6)	908(5.3)	<0.001
Offered brief or extended advice	314(18.1)	892(5.2)	
Offered Referral	19(1.1)	14(0.1)	
Offered Both	17(1.0)	2(0.03)	
Data not recorded	1,381(80.4)	16,402(94.7)	
¹ Chi squared tests p value			

Table 6-9 Proportion and OR (95% CIs) of patients with any alcohol intervention record, stratified by age.

	Cases n=1,731	Controls n=17,310	OR(95% CI)*
Overall	340(19.6)	908(5.3)	3.7(2.9-4.6) ^a
Age at diagnosis			
18-44	109(18.3)	228(3.8)	4.3(3.1-5.8)
45-54	76(22.8)	198(5.9)	3.2(2.2-4.8)
55-64	72(21.5)	185(5.8)	3.7(2.7-5.2)
65-74	63(26.7)	167(7.2)	3.8(2.7-5.2)
≥ 75	30(12.9)	130(5.3)	2.4(1.5-3.7)
^a OR adjusted for age, sex and consulting rate			
*adjusted for sex and consulting rate, unless otherwise stated			
LRT for sex interaction p value: 0.06			
LRT for age interaction p value: 0.02			

6.3 Discussion and interpretation

6.3.1 Summary of findings

This study has shown that rates of health service utilisation are up to 4 times higher among people with alcoholic psychosis as far as 10 years before diagnosis, compared to the control population. It also shows that 4 in every 5 cases had had a previous discussion about their alcohol use with their general practitioner and of these, half had been identified as drinking at harmful or hazardous levels. However, records of any prior alcohol brief intervention or referral were found for less than 20% of cases. Overall men with alcoholic psychosis appeared to be more likely than women to have had a discussion about their alcohol use in primary care, but were as likely as women to have been offered alcohol related interventions.

6.3.2 Strengths and limitations

This is the first longitudinal study to comprehensively describe primary and secondary care use among people who go on to develop alcoholic psychosis compared with a representative general population control group, and is also the first to use nationally representative linked primary and secondary care records for this purpose. Using the linkage between CPRD and HES has enabled the identification of a comprehensive population of patients with alcoholic psychosis. Based on the findings in chapter 3, using either primary care or secondary care data alone would have significantly underestimated the number of patients with this condition. Cases of alcoholic psychosis were frequency matched to controls on age and general practice. Therefore the potential effect of age and variations in general practice on healthcare utilisation estimates has been minimised (174).

A potential weakness of this study is the issue of the diagnostic validity of alcoholic psychosis used in this thesis. Although evidence supporting alcoholic psychosis diagnosis was found for 89% of cases i.e. 89% of patients with a diagnosis in either HES or CPRD have a diagnostic or prescription record in the alternate dataset to substantiate their diagnosis, 11%(n=192) still do not have any supportive evidence. An alternative and more sensitive way to validate diagnosis would have been to directly obtain and examine paper records from GP's for any confirmatory information relating to the diagnosis of alcoholic psychosis. However, this is time consuming and very expensive (approximately £100 per validated subject) and due to limited resources, it was not possible to validate diagnoses in this way for this thesis. Given that there are specific criteria for diagnosing alcoholic psychosis as shown in the fifth Edition of the Diagnostic and Statistical Manual of Mental disorders(DSM-V) (206,207), it is plausible to assume that general practitioners are unlikely to record this diagnosis in error and this potential issue of validity, if it exists, is unlikely to have significantly impacted on the study findings.

Owing to the previously discussed limitations of recording of alcohol related events within the CPRD dataset, it is possible that the proportion of patients with alcoholic psychosis who were asked about their alcohol use or offered interventions has been underestimated in this study. Thus more attention should be given to relative intervention rates between different groups (cases vs controls, males vs females, different age groups) rather than absolute rates, as the former highlight intervention gaps which are likely not to be accounted for by recording limitations, but remain important to highlight in order to effect change and improvements in clinical practice. In the study analysis, there were no adjustments for some important variables (e.g. socioeconomic status, and ethnicity) which may affect alcohol use enquiry or healthcare utilisation thus unmeasured confounding cannot be excluded. Nonetheless,

the impact of other potential confounding variables on alcohol use enquiry such as sex and consulting rate were assessed to minimise potential confounding.

6.3.3 Implications for clinical practice

The findings of this study have shown that practitioners in the UK inquire about alcohol consumption during healthcare visits in a high proportion of patients who subsequently develop alcoholic psychosis. However, on the other hand, results on interventions show a relatively low proportion of patients with any record of an intervention offer. Considering that primary care is a gatekeeper for healthcare in the UK, the low numbers of intervention records could have an important long term impact whereby hospital and mental health services increasingly see patients with illnesses that could otherwise have been averted at a much earlier stage.

While this low rate of recorded interventions may mean that treatment of alcohol problems in the UK is suboptimal, it could also be that there may be a failure to record treatments delivered to patients or also important, that appropriate treatment services are not consistently available within health service centres for practitioners to make onward referral of high risk patients. Together these reasons imply that more can be done in the UK to prevent alcoholic psychosis.

One way of addressing the deficit in recording or intervening as previously suggested could be by regularly training healthcare professionals in detecting, recording and intervening for alcohol use as part of routine practice (208–210). Such training could improve practitioners feeling of competence in dealing with problem drinking and could also serve as a refresher course to remind practitioners about the benefits of intervening early for alcohol problems. In addition, providing practitioners with specific training in mental health could also prove beneficial. Previous studies have shown

deficits in the ability of primary care practitioners to detect mental health disorders with some studies showing between 20% and 90% of patients with mental health disorders being undetected by primary care practitioners(211–214). Undoubtedly, such lack of awareness of the disease risk in a patient in the first instance would result in a delay in the decision to conduct screening for substance abuse.

Lack of financial support is often cited by practitioners as a barrier to enquiry about and recording of alcohol use, therefore there is also the possibility that pay for performance policies which can incentivise practitioners for enquiring and intervening for people's alcohol consumption may lead to increased intervening and recording. Currently in the UK, such scheme of incentives exists for recording of smoking status and has been shown to be effective but remains patchy for alcohol related activity.

Another aspect of the presented results for which there are important implications is the finding that women with alcoholic psychosis were less likely than men to have a record of alcohol use. This is likely to impact negatively on strategies that treat alcohol problems on a population level since women are reported to be more vulnerable to alcohol related consequences (e.g. alcoholic liver disease, and fetal alcohol syndrome) and may therefore continue to contribute to increasing rates of such diseases if they are missed by early treatment services (188,189).

6.3.4 Chapter conclusions

The findings of the study show a higher excess of healthcare use in cases of alcoholic psychosis compared with the general population and greater excesses are seen in men than women. While a high proportion of cases were asked about their alcohol use during these healthcare visits, few patients had records of interventions and men were

more likely than women to have an alcohol record. Given the potential effectiveness of screening and brief alcohol intervention to reduce risky drinking behaviour and the significant morbidity impact of mental health disorders, these findings should encourage healthcare professionals to target alcohol interventions more often at people who are at risk. Additionally, given that mental health is at the core of current healthcare reforms (215), these findings should encourage policy makers to direct more effort towards improving practitioners' ability to detect and treat alcohol use as this could contribute towards the governments mandate to the NHS to reduce mental health problems and could also have an overall positive impact on mental health morbidity and mortality in the UK.

Chapter 7

7 Alcohol-attributable morbidities present in patients before the diagnosis of alcoholic psychosis

7.1 Introduction

The causes of excess healthcare utilisation prior to the diagnosis of alcoholic psychosis are poorly understood but may help practitioners in the early identification of those who may benefit the most from targeted preventive interventions. This study aimed to estimate what the burden of diseases that are reported to be partly alcohol attributable are in patients during the time leading up to alcoholic psychosis diagnosis and the frequency of occurrence of these diseases in these patients compared to the general population.

7.2 Methods

7.2.1 Data

Data used were from the linked Clinical Practice Research Datalink and Hospital Episodes Statistics described in Chapter 2.

7.2.2 Population

The incident cases of alcoholic psychosis and the controls identified in CPRD and HES for the previous study were used for this study.

7.2.3 Observation period

The study start date for each patient was the latest of (i) the start of the linked dataset (1st April 1997), (ii) the date a patient registered with a GP practice, or (iii) the date

when the practice attained an acceptable level of data recording, whichever came first. The study end date was the date of alcoholic psychosis diagnosis/ pseudo-diagnosis.

7.2.4 Identifying partly alcohol-attributable morbidity in primary and secondary care

As described in chapter 5 the list of conditions considered to be partly attributable to alcohol was based on England's national guide for alcohol-attributable fractions which has been validated against other international sources (196,216). The same method described therein was also used to identify the presence of these diagnoses in the alcoholic psychosis study population.

7.2.5 Covariates

Data on patient sex, age, smoking history and alcohol use were extracted from CPRD as described in chapter 3.

7.2.6 Missing data

Missing data on smoking or alcohol use was addressed by including a "no data available" category so that such patients were not excluded from the analyses.

7.2.7 Statistical analysis

Baseline characteristics of cases and controls were described using descriptive statistics and compared via chi squared tests. Proportions were calculated for the number of patients that were ever previously diagnosed with an alcohol-attributable condition and those with one, two or three or more different conditions. The frequency of each specific condition and each ICD category among cases and controls was also calculated. The number of people identified as ever having a diagnosis was used as the numerator and the number of patients with alcoholic psychosis or controls as the denominator.

Logistic regression was used to explore the association between each ICD category and alcoholic psychosis; results are presented as odds ratios (OR) and 95% confidence intervals (CI). The potential for effect modification by age and sex on this association was also tested for via stratified analyses and the fitting of interaction terms using logistic regression with the significance of models tested using likelihood ratio tests (LRTs) and $p < 0.05$ considered significant.

To investigate whether the occurrence of each condition varied at different times before psychosis diagnosis, frequencies and odds ratios (unadjusted and adjusted for age, sex and smoking status) were recalculated for each condition for the four predefined pre-diagnosis exposure periods. Not all patients were included in this analysis. Restriction was applied based on completeness of follow up such that the analyses for any time period were limited to those with complete follow up. For example, only patients with a minimum of 2 years' worth of pre-diagnosis data were included in 13 months to 2 year time period analyses. Likewise, only individuals with up to 5 years and up to 10 years' worth of pre diagnosis data were included in the 3 to 5 year and 6 to 10 year time periods respectively.

All analyses were conducted using the statistical software Stata v12.0 (StataCorp, Texas).

7.3 Results

As previously described, the study population comprised of 1,731 cases of alcoholic psychosis diagnosed in primary or/and secondary care between 1997 and 2014, and 17,310 controls (Table 7-1).

Table 7-1 Baseline characteristics of the alcoholic psychosis study population.

	Cases n=1,731	Controls n=17,310	P value¹
Age at diagnosis(years)			
Mean(SD)	53.3(17.3)	53.2(17.5)	0.55*
Age group (n, %)			
min-44	595(34.4)	5,999(34.7)	0.79
45-54	334(19.3)	3,375(19.5)	
55-64	335(19.4)	3,170(18.3)	
65-74	236(13.6)	2,325(13.4)	
≥ 75	231(13.3)	2,441(14.1)	
Observation time(years)			
Median(IQR)	5.5(2.6-9.2)	4.4(2.3-8.2)	
Up to 12months	1,731(100)	17,371(100)	
Up to 2years	1,444(83.4)	13,789(79.7)	
Up to 5years	912(52.7)	7,779(44.9)	
Up to 10 years	362(20.9)	2,901(16.8)	
Sex (n, %)			
Male	1,156(66.8)	8,481(49.0)	0.001
Female	575(33.2)	8,829(51.0)	
Smoking status			
Non smoker	317(18.3)	7,089(40.9)	<0.001
Current smoker	875(50.6)	3,599(20.8)	
Ex-smoker	258(14.9)	2,953(17.1)	
No recorded data	281(16.2)	3,669 (21.2)	
Alcohol use status			
			<0.001
Never	54(3.1)	1,871(10.8)	
Moderate	298(17.2)	7,316(42.3)	
Hazardous/harmful	881(50.8)	1,496(8.6)	
Unclear	136(7.9)	643(3.7)	
No recorded data	362(20.9)	5,984(34.6)	

*Ttest p value ¹ chi squared test p value unless indicated otherwise

7.3.1 Alcohol attributable healthcare attendances

Table 7-2 shows the proportions of patients who presented to primary or secondary care with at least one partially alcohol-attributable condition during the study period.

A total of 1,104 cases (63.8%) had presented with at least one condition partially attributable to alcohol during a preceding primary care or hospital visit, compared to 31.1% in the control population. There was a four-fold risk of patients being later diagnosed with alcoholic psychosis associated with presenting with any alcohol-attributable morbidity. Alcoholic psychosis risk was found to increase with increasing numbers of morbidity; from over three-fold in those with one morbidity (OR 3.3, 95% CI [2.9-3.7]) to over ten-fold in those with three or more morbidities (OR 10.2, 95% CI [7.9-13.1]).

Table 7-2 Proportions of patients with at least one partially alcohol-attributable condition at any point during the study, with OR (95% CI) comparing cases to controls.

	Cases (n=1,731)	Controls (n =17,310)	OR (95% CI)
Any GP or hospital diagnosis of partly alcohol attributable condition			
Yes	1,104(63.8)	5,376(31.1)	3.9(3.5-4.3)
1*	719(65.1)	4,107(76.4)	3.3(2.9-3.7)
2*	284(25.7)	1,081(20.1)	5.0(4.3-5.8)
3 or more*	101(9.2)	188(3.5)	10.2(7.9-13.1)
No	627(36.2)	11,934(68.9)	

Table 7-3 shows proportions of patients seen for at least one attributable condition stratified by age and sex.

Across age groups, stronger associations with alcoholic psychosis was seen for younger patients (OR for those <45 years 6.6, 95% CI [5.5-7.9]) who had presented with an attributable morbidity compared to older patients (OR for those >75years 1.9, 95% CI [1.4-2.6]).

Comparing associations by sex, there was no substantial difference in risk of alcoholic psychosis between men (OR 4.0, 95% CI [3.6-4.6]) and women (OR 3.9, 95% CI [3.2-4.6]) who had presented previously with an alcohol-attributable morbidity.

Table 7-3 Proportion of patients with at least one partially alcohol-attributable condition at any point during the study, with OR (95% CI) comparing cases to controls, stratified by sex and age.

	Cases n=1,731	Controls n=17,310	Odds ratios (95% CI)
Sex			
Male			
No	423(36.6)	5,934(69.9)	
Yes	733(63.4)	2,547(30.0)	4.0(3.6-4.6)
Female			
No	204(35.5)	6,000(68.0)	3.9(3.2-4.6)
Yes	371(64.5)	2,829(32.0)	
Age groups			
18-44			
No	250(42.0)	4,964(82.8)	
Yes	345(57.9)	1,035(17.3)	6.6(5.5-7.9)
45-54			
No	139(41.6)	2,577(76.4)	
Yes	195(58.4)	798(23.6)	4.5(3.6-5.7)
55-64			
No	118(35.2)	2,082(65.7)	
Yes	217(64.8)	1,088(34.3)	3.5(2.8-4.5)
65-74			
No	56(23.7)	1,274(54.8)	
Yes	180(76.3)	1,051(45.2)	3.9(2.9-5.3)
≥ 75			
No	64(27.7)	1,037(42.5)	
Yes	167(72.3)	1,404(57.5)	1.9(1.4-2.6)
LRT for interaction between sex and the likelihood of presenting with an alcohol-attributable condition: p =0.68			
LRT for interaction between age and the likelihood of presenting with an alcohol-attributable condition: p < 0.0001			

Table 7-4 shows proportions and OR for each ICD 10 disease group.

All assessed disease groups but malignant neoplasms were significantly higher in cases than controls. The most common disease categories among cases were injuries (49.5%), cardiovascular diseases (22.9%) and nervous system disease (7.7%) corresponding to adjusted odds ratios of 5.7 (95% CI [5.1-6.4]), 1.7 (95% CI [1.5-1.9]) and 7.1 (95%CI [5.6-9.0]).

Of all diseases, nervous system disease (OR 7.1, 95%CI 5.6-9.0) and Injuries (OR 5.7, 95% CI 5.1-6.4) had the strongest association with alcoholic psychosis. Digestive disease was relatively uncommon but had the third strongest association with alcoholic psychosis (OR 3.2, 95% CI 2.4 - 4.2).

Table 7-4 **Prevalence of partly alcohol attributable conditions by ICD-10 group**

	Cases (n=1,731) n (%)	Controls (n=17,310) n (%)	Unadjusted OR (95% CI)	Adjusted OR(95% CI)
Malignant neoplasms	27(1.6)	230(1.3)	1.2 (0.8-1.8)	1.4(0.9-2.1)
Diabetes	127 (7.3)	923 (5.3)	1.4(1.2-1.7)	1.3(1.1-1.7)
Nervous system diseases	134 (7.7)	201(1.6)	7.1 (5.7-8.9)	7.1(5.6-9.0)
Cardiovascular diseases	396(22.9)	2,697(15.6)	1.6 (1.4 -1.8)	1.7(1.5-1.9)
Digestive diseases	72(4.2)	253(1.5)	2.9(2.2-3.8)	3.2(2.4-4.2)
Injuries	857 (49.5)	2,546(14.7)	5.7(5.1-6.3)	5.7(5.1-6.4)

Table 7-5 and Figure 7-1 shows the proportions of cases and controls with each morbidity stratified by age.

There was a marked variation in the magnitude of effect across age groups for most diseases (Table 7-5 and Figure 7-1). The odds of malignant neoplasms, diabetes and cardiovascular disease for instance generally decreased with increasing age, and the highest odds was seen among those who were less than 45 years old. For nervous system and digestive disease, odds of alcoholic psychosis were highest for those aged 45-54years, while for injuries all age groups less than 75years had comparatively similar odds.

Table 7-5 Proportions by ICD-10 group stratified by age.

	Cases (n=1,731) n (%)	Controls (n=17,310) n (%)	Unadjusted OR (95% CI)	Adjusted OR(95% CI)
Malignant neoplasms	27(1.6)	230(1.3)	1.2 (0.8-1.8)	1.4(0.9-2.1)
min-44	-	-	-	-
45-54	6(1.8)	23(0.7)	2.7(1.1-6.6)	3.6(1.3-9.6)
55-64	7(2.1)	61(1.9)	1.1(0.5-2.4)	1.4(0.6-3.2)
65-74	6(2.5)	63(2.7)	0.9(0.4-2.2)	1.1(0.5-2.7)
≥ 75	8(3.5)	78(3.2)	1.1(0.5-2.3)	1.1(0.5-2.4)
Diabetes	127 (7.3)	923 (5.3)	1.4(1.2-1.7)	1.3(1.1-1.7)
min-44	13(2.2)	58(0.9)	2.3(1.2-4.2)	2.2(1.1-4.2)
45-54	20(5.9)	126(3.7)	1.6(1.0-2.7)	1.8(1.1-2.9)
55-64	34(10.2)	210(6.6)	1.6(1.1-2.3)	1.5(1.0-2.2)
65-74	31(13.1)	233(10.2)	1.4(0.9-2.0)	1.3(0.9-1.9)
≥ 75	29(12.6)	296(12.1)	1.0(0.7-1.6)	0.9(0.6-1.4)
Nervous system diseases	134 (7.7)	201(1.6)	7.1 (5.7-8.9)	7.1(5.6-9.0)
min-44	47(7.9)	70(1.1)	7.3(4.9-10.6)	7.8(5.1-11.8)
45-54	36(10.7)	39(1.2)	10.3(6.5-16.5)	11.0(6.5-18.7)
55-64	31(9.3)	28(1.2)	8.4(5.2-13.7)	7.5(4.4-12.8)
65-74	10(4.2)	28(1.2)	3.6(1.7-7.6)	3.7(1.7-7.9)
≥ 75	10(4.3)	26(1.1)	4.2(2.0-8.8)	3.9(1.9-8.5)
Cardiovascular diseases	396(22.9)	2,697(15.6)	1.6 (1.4 -1.8)	1.7(1.5-1.9)
min-44	36(6.1)	127(2.1)	3.0(2.0-4.4)	3.0(2.0-4.6)
45-54	66(19.8)	314(9.3)	2.4(1.8-3.2)	2.5(1.8-3.5)
55-64	104(31.0)	618(19.5)	1.9(1.5-2.4)	1.8(1.4-2.3)
65-74	95(40.3)	683(29.4)	1.6(1.2-2.1)	1.5(1.2-2.0)
≥ 75	95(41.1)	955(39.1)	1.1(0.8-1.4)	0.9(0.7-1.3)
Digestive diseases	72(4.2)	253(1.5)	2.9(2.2-3.8)	3.2(2.4-4.2)
min-44	12(0.2)	46(0.8)	2.7(1.4-5.1)	3.2(1.6-6.3)
45-54	23(6.9)	34(1.0)	7.3(4.2-12.5)	7.2(3.9-13.3)
55-64	16(4.8)	51(1.6)	3.1(1.7-5.4)	3.5(1.9-6.5)
65-74	13(5.5)	67(2.9)	1.9(1.1-3.6)	2.4(1.3-4.4)
≥ 75	8(3.5)	55(2.3)	1.6(0.7-3.3)	1.4(0.6-2.9)
Injuries	857 (49.5)	2,546(14.7)	5.7(5.1-6.3)	5.7(5.1-6.4)
min-44	317(53.3)	806(13.4)	7.3(6.2-8.8)	6.5(5.4-7.8)
45-54	147(44.0)	407(12.1)	5.7(4.5-7.3)	5.1(3.9-6.7)
55-64	148(44.2)	391(12.3)	5.6(4.4-7.2)	6.2(4.7-7.9)
65-74	122(51.7)	338(14.5)	6.3(4.8-8.3)	6.7(5.0-9.0)
≥ 75	123(53.3)	604(24.7)	3.5(2.6-4.6)	3.9(2.9-5.2)

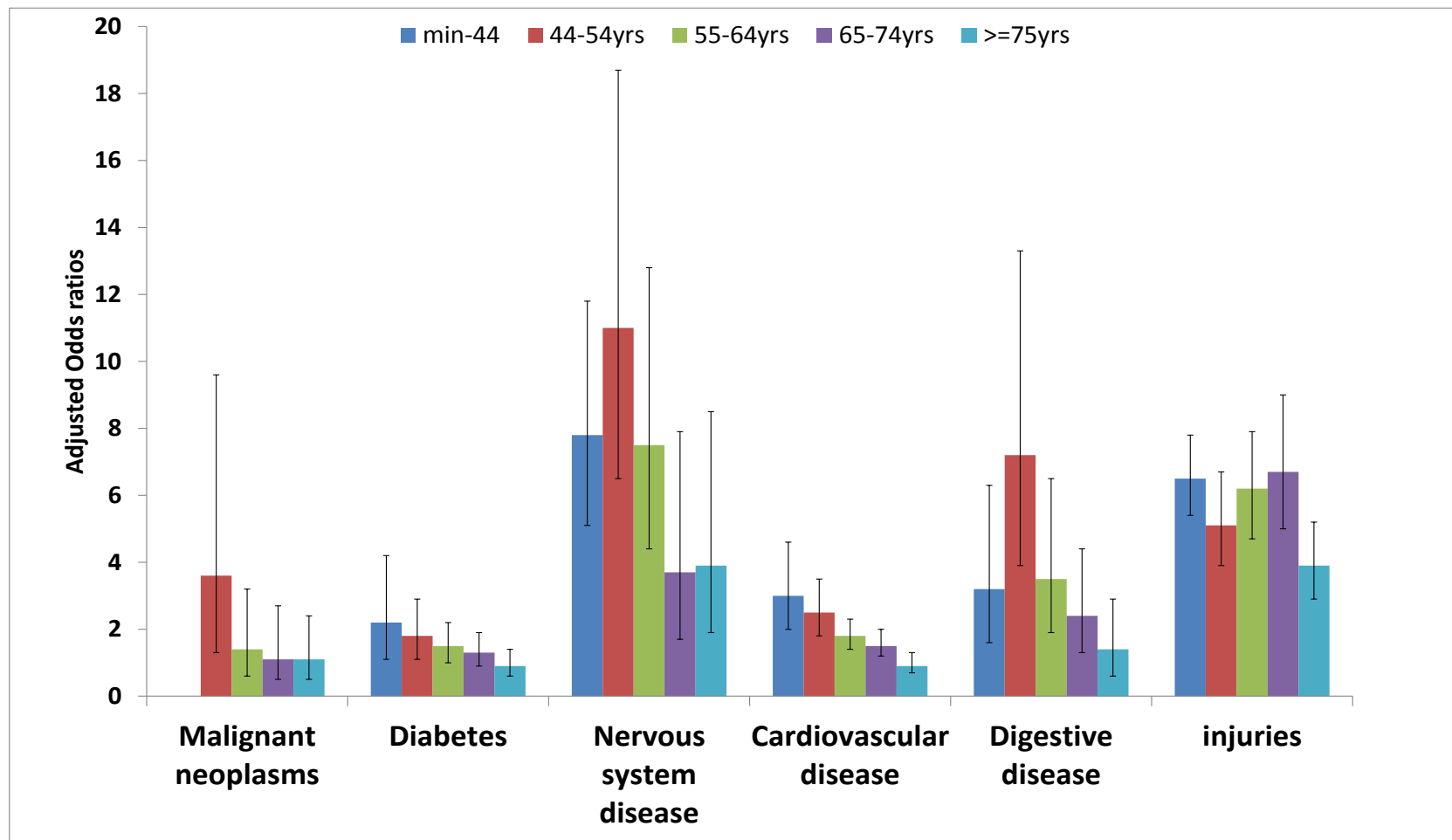


Figure 7-1 Adjusted Odds ratios for alcohol attributable morbidities, stratified by age

Table 7-6 shows proportions and odds ratios computed for each condition within each of the six ICD categories. Due to small numbers the different injuries assessed were simply grouped into intentional or unintentional injuries.

Assessing proportions for the individual conditions within each ICD 10 category showed that within each category, certain conditions were more strongly associated with subsequent diagnosis of alcoholic psychosis than others. For example, within the cardiovascular disease category, cerebrovascular diseases had the strongest association with alcoholic psychosis (Adjusted OR 2.8, 95% CI [2.3-3.5]) compared to hypertension (adjusted OR 1.1, 95% CI [0.9-1.3]) or Ischaemic heart disease (adjusted OR 1.7, 95% CI [1.4-2.1]).

Among injuries, intentional injuries and self-harm (Adjusted OR 11.8, 95% CI [9.8-14.1]) were more strongly associated with subsequent diagnosis with alcoholic psychosis than unintentional injuries (OR 4.5, 95% CI [4.0-5.0]) (Table 7-6).

Table 7-6 Proportions and ORs for each morbidity for cases and controls

Conditions	Cases (n=1,731)	Controls (n=17,310)	OR (95% CI)	
			Unadjusted	Adjusted'
Malignant neoplasms of:				
Larynx	-	-	-	-
Colon and rectum	8(0.5)	71(0.4)	1.1(0.5-2.3)	1.2(0.5-2.5)
Breast	12(0.7)	130(0.8)	0.9(0.5-1.7)	1.6(0.9-2.9)
Oesophagus	-	-	-	-
Lip, oral cavity and pharynx	5(0.3)	20(0.1)	2.5(0.9-6.7)	1.6(0.6-4.5)
Diabetes^	127(7.3)	923(5.3)	1.4(1.2-1.7)	1.4(1.1-1.7)
Diseases of the nervous system				
Epilepsy and Status epilepticus	134(7.7)	201(1.2)	7.1(5.7-8.9)	7.0(5.5-8.9)
Cardiovascular diseases				
Cardiac arrhythmias	43(2.5)	219(1.3)	1.9(1.4-2.8)	1.9(1.4-2.8)
Cerebrovascular diseases	118(6.8)	436(2.5)	2.8(2.3-3.5)	2.8(2.3-3.5)
Hypertensive diseases	178(10.3)	1,697(9.8)	1.0(0.9-1.2)	1.1(0.9-1.3)
Ischaemic heart disease	162(9.4)	901(5.2)	1.9(1.6-2.2)	1.7(1.4-2.1)
Digestive diseases				
Pancreatitis	37(2.1)	37(0.2)	10.2(6.4-16.1)	8.5(5.2-13.8)
Cholelithiasis	38(2.2)	232(1.3)	1.7(1.2-2.3)	1.9(1.4-2.9)
Injuries				
Unintentional injuries*	712(41.1)	2,381(13.8)	4.4(3.9-4.9)	4.5(4.0-5.0)
Intentional injury/self-harm+	326(18.8)	290(1.7)	13.6(11.5-16.1)	11.8(9.8-14.1)

*Unintentional injuries include falls, fractures, asphyxia, road traffic accidents and unintentional poisonings.

+Intentional injuries include assault, intentional self-harm and intentional poisoning ^excludes gestational diabetes

'adjustment for age, sex and smoking status

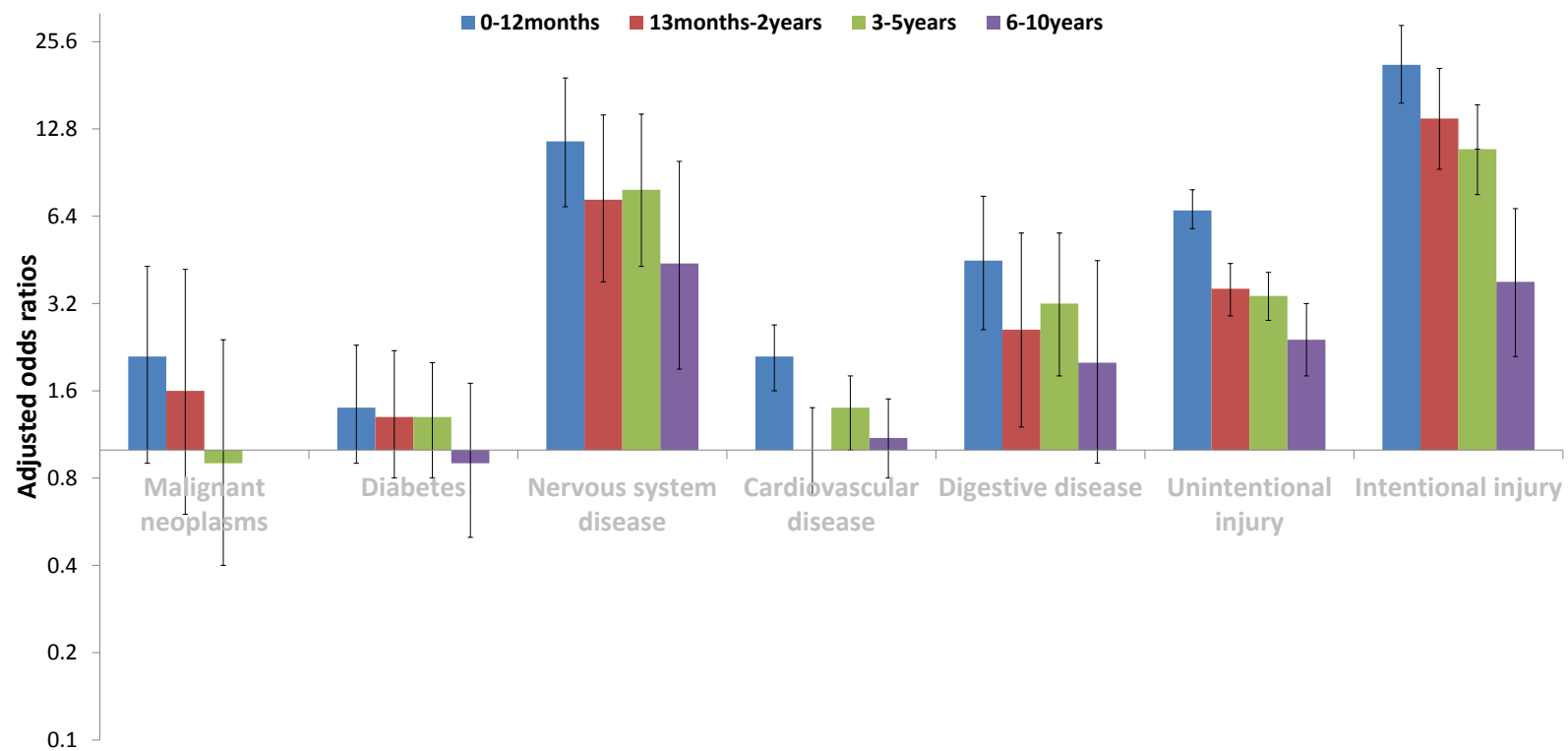
Table 7-7 and Figure 7-2 shows proportions and ORs for each morbidity at different time periods.

There were variations in the odds of the various conditions over time (Table 7-7 and Figure 7-2). The odds of all diseases were significantly higher in cases than in the control population around the time of psychosis diagnosis than at other times. The only exceptions were diabetes and malignancies where cases were as likely as controls to present with each disease in all time periods. Injuries (unintentional and intentional) and epileptic seizures retained very strong associations even as far as 10 years before diagnosis but ORs for the association between cardiovascular disease with alcoholic psychosis were not significant in the time periods earlier than the year of diagnosis.

Table 7-7 The proportion of patients presenting with each examined condition at different periods before psychosis diagnosis with OR (95% CI) comparing cases to controls.

Time to diagnosis	At risk cases n(%)	At risk controls n(%)	OR (95% CI)	
			Unadjusted	Adjusted'
Malignant neoplasms				
0-12months	9(0.5)	50(0.3)	1.8(0.9-3.7)	2.1(0.9-4.3)
13mths- 2yrs	5(0.4)	41(0.3)	1.2(0.5-2.9)	1.6(0.6-4.2)
3-5yrs	5(0.6)	53(0.7)	0.8(0.3-2.0)	0.9(0.4-2.4)
6-10yrs	-	23(0.8)	-	-
Diabetes				
0-12months	23(1.3)	153(0.9)	1.5(0.9-2.3)	1.4(0.9-2.3)
13mths- 2yrs	17(1.2)	120(0.9)	1.4(0.8-2.3)	1.3(0.8-2.2)
3-5yrs	26(2.9)	163(2.1)	1.4(0.9-2.1)	1.3(0.8-2.0)
6-10yrs	13(3.6)	93(3.2)	1.1(0.6-2.0)	0.9(0.5-1.7)
Nervous system diseases				
0-12months	38(2.2)	34(0.2)	11.4(7.2-18.1)	11.6(6.9-19.2)
13mths- 2yrs	19(1.3)	23(0.2)	7.9(4.3-14.7)	7.3(3.8-14.3)
3-5yrs	24(2.6)	26(0.3)	8.1(4.6-14.1)	7.9(4.3-14.4)
6-10yrs	12(3.3)	17(0.5)	5.8(2.8-12.3)	4.4(1.9-9.9)
Cardiovascular diseases				
0-12months	88(5.1)	415(2.4)	2.2(1.7-2.8)	2.1(1.6-2.7)
13mths- 2yrs	40(2.8)	360(2.6)	1.1(0.8-1.5)	1.0(0.7-1.4)
3-5yrs	85(9.3)	550(7.1)	1.4(1.1-1.7)	1.4(1.0-1.8)
6-10yrs	51(14.1)	324(11.2)	1.3(0.9-1.8)	1.1(0.8-1.5)
Digestive diseases				
0-12months	22(1.3)	57(0.3)	3.9(2.4-6.4)	4.5(2.6-7.5)
13mths- 2yrs	9(0.6)	36(0.3)	2.4(1.2-4.9)	2.6(1.2-5.6)
3-5yrs	18(1.9)	61(0.8)	2.5(1.5-4.3)	3.2(1.8-5.6)
6-10yrs	8(2.2)	33(1.1)	2.0(0.9-4.3)	2.0(0.9-4.5)
Unintentional injuries				
0-12months	332(19.2)	621(3.6)	6.4(5.5-7.4)	6.7(5.8-7.9)
13mths- 2yrs	172(11.9)	482(3.5)	3.7(3.1-4.5)	3.6(2.9-4.4)
3-5yrs	217(23.8)	657(8.5)	3.4(2.8-4.0)	3.4(2.8-4.1)
6-10yrs	87(24.0)	331(11.4)	2.5(1.9-3.2)	2.4(1.8-3.2)
Intentional injury/self-harm				
0-12months	158(9.1)	68(0.4)	25.5(19.1-34.0)	21.3(15.7-29.1)
13mths- 2yrs	75(5.2)	46(0.3)	16.4(11.3-23.7)	13.9(9.3-20.7)
3-5yrs	93(10.2)	65(0.8)	13.5(9.7-18.7)	10.9(7.6-15.5)
6-10yrs	22(6.1)	37(1.3)	5.0(2.9-8.6)	3.8(2.1-6.8)
Numbers at risk within each analyses time period				
0-12months	1,731(100)	17,371(100)		
13months-2years	1,444(83.4)	13,789(79.7)		
3-5years	912(52.7)	7,779(44.9)		
6-10years	362(20.9)	2,901(16.8)		

^a adjustment for age, sex and smoking status - number within cell <5

Figure 7-2 Adjusted odds ratios for each alcohol attributable morbidity, stratified by time

7.4 Discussion and Interpretation

7.4.1 Summary of findings

This study demonstrates that compared with patients in the general population, those patients who acquire a diagnosis of alcoholic psychosis attend both primary and secondary health care providers more frequently with other conditions reported to be attributable to alcohol. The conditions with the highest frequency in cases were injuries (unintentional and intentional) and nervous system disease (epilepsy), and the risk of both diseases was substantially higher in cases than in the general population as far as 10 years before alcoholic psychosis diagnosis. The third strongest association with alcoholic psychosis was seen for digestive diseases, and this association was apparent up to 5 years before diagnosis.

Patients younger than 45 years appeared to have the highest odds of all diseases. However the odds of intentional and unintentional injuries remained high across all age groups.

Together, these results suggest that targeting individuals with any alcohol-attributable disease may be beneficial in identifying high risk patients, and specifically focussing on those who present with any of these three conditions (digestive diseases, intentional injuries and epilepsy) may be a more sensitive way of identifying people who will be more likely to develop alcoholic psychosis.

7.4.2 Strengths and limitations

This is the first longitudinal study to assess not only alcohol related morbidities in patients prior to alcoholic psychosis but also the patterns of these morbidities as they vary over time and across age groups. Other general strengths of the study include the fact that the data on morbidities were prospectively collected, thus the possibility of

recall bias can be excluded. The large sample size of the study means that there was sufficient statistical power to generate effect estimates for morbidity categories that comprised of relatively few participants. By frequency matching the control group on general practice and age to cases, it was possible to account for differences in data recording between practices and differences in healthcare seeking behaviour between age groups respectively and this also provided the opportunity to assess for interaction by age where it occurred. Adjustment for several potential confounders implies that the study estimates are reasonably robust. Furthermore, by using general population and HES data which have national coverage, the study results are reasonably generalizable to the English population.

Despite these strengths, there are some limitations and potential explanations of the study findings which warrant discussion. As mentioned in the previous chapter, there is the issue of the validity of alcoholic psychosis diagnosis which may have affected the robustness of the disease definition used in this study; however validation attempts were made to verify that patients identified had some evidence to substantiate their diagnosis. There is also the issue of unmeasured or residual confounding, since the lack of information on other potential modifiers of healthcare use, for e.g. socio-economic status, education and family history, meant that these were not adjusted for. The most important limitation of this study, however, is that there isn't enough information to explicitly exclude the potential for reverse causality bias. For example, with specific regards to self-harm injuries it is possible that patients may have had "mild" or subclinical psychotic symptoms which lead to self-harm even before harmful or hazardous drinking began. Although analysis separated by time still showed that the relationships go as far back as 10 years pre-diagnosis of alcoholic psychosis, it is still not entirely clear what the subclinical ill-health among these patients were prior to the

study or prior to alcoholic psychosis diagnosis therefore these findings need to be interpreted with caution.

Cautious interpretation is also required for the strong association observed between alcoholic psychosis and epilepsy. It could be argued that this finding is explained by the general increased risk of any psychosis that is present in patients with epilepsy(217,218). In one population survey in Sweden which included 713 adults with active epilepsy for instance, 5.9% of patients were reported to have had psychoses, alcohol dependence syndrome or other psychiatric disorders. In another study of 987 patients with epilepsy in Iceland, lifetime prevalence of psychosis of 6% and 9% was also found for males and females respectively. Higher prevalence of up to 10-20% are also reported in patients with refractory epilepsy and even twice as high this proportion has been reported in patients with idiopathic generalized epilepsy. An alternative explanation could also be misclassification bias whereby withdrawal seizures in some patients may have been misdiagnosed as epilepsy thus resulting in the relatively high prevalence of the disease in cases.

7.4.3 Interpretation in the context of other studies

While there are very few reports to which these findings can be compared to, the present study findings of high rate of alcohol-related comorbidity are similar to a previous Finnish study by Perala et al that looked at both the psychiatric and alcohol-related morbidities in patients prior to psychosis diagnosis(84). In Perala et al, the prevalence of lifetime treatment for head injuries, fractures, gastritis, epilepsy, fractures and arrhythmias was reported and was found to be higher among cases than a control population of people without alcohol dependence. The reported study however adds more information to this by describing, in addition to the conditions already mentioned by Perala et al, the prevalence of much more comprehensive

categories of diseases, overall and at different pre-diagnosis periods and by using a much larger population than previously. The association between alcoholic psychosis and these morbidities are simply explained by the widely reported interrelationship between these diseases and alcoholism(87).

7.4.4 Chapter conclusions and implications

This study quantified the burden of alcohol related comorbidities in patients diagnosed with alcoholic psychosis. Nearly two thirds of cases had had an alcohol-related condition compared to 31% in the control group. The association between several comorbidities (e.g. intentional and unintentional injuries) and psychosis diagnosis was strong as far as 10 years before psychosis diagnosis, implying that a closer review of alcohol-attributable healthcare attendances may be able to ensure the timely identification and treatment of patients who are currently at high risk of alcohol related mental problems. Patients who are identified early could be provided with potentially effective interventions that help modify drinking behaviour in addition to psychotherapeutic and pharmacologic interventions that target prodromal psychotic symptoms. Together such interventions may help delay the onset of psychosis in alcoholics and possibly avert the occurrence of the disease altogether.

Chapter 8

8 Thesis summary, conclusions and recommendations for future research

8.1 Summary

This thesis sought to investigate whether there are opportunities within primary and secondary care settings to identify, treat or improve the prevention of alcohol misuse and its associated disorders. The first part looked at opportunities for prevention in people with alcoholic cirrhosis, while the second part looked at the same outcomes in people with alcoholic psychosis. For both disease groups, there were three objectives:

- 1) To describe rates of healthcare utilisation (a proxy for intervention opportunities) in comparison to a control population during the pre-diagnosis period.
- 2) To estimate the proportion of people with records of alcohol consumption or interventions in order to highlight if there is room to improve current prevention practice.
- 3) To quantify comorbidities in patients during the pre-diagnosis period, as this is important to identify any specific alcohol related sequelae in patients that could inform future case finding strategies.

Alcoholic cirrhosis and psychosis were specifically selected as they represent chronic alcoholism and are associated with significant morbidity and mortality. In addition, by making use of these two particular disease groups, this thesis had the opportunity to assess two slightly different populations of heavy drinkers in the UK. Compared to the population of patients with alcoholic psychosis, the alcoholic cirrhosis population were of a slightly older age and had more men.

Summary of main findings

Overall, the thesis findings were generally consistent across both alcoholic cirrhosis and psychosis and are as follows:

- Patients with alcoholic cirrhosis and alcoholic psychosis had a substantially higher rate of GP consultations and hospital admissions compared to the general population, particularly in the 5 years immediately before diagnosis.
- The excess healthcare utilisation rates associated with alcoholic cirrhosis and psychosis were higher in men than women.
- Although a high proportion of patients with cirrhosis and psychosis were being asked about their alcohol use, a large number of identified heavy drinkers were recorded to have not been given alcohol use interventions.
- There was high prevalence of previously diagnosed alcohol-attributable morbidities among patients with alcoholic cirrhosis and psychosis which may explain the excess use of healthcare services among these patients.
- In general, the risks of developing either alcoholic cirrhosis or psychosis increased with the increasing number of previously diagnosed morbidities, such that patients with 3 or more conditions had a relative risk of between a 9-10 fold compared to 3 fold in those with single morbidity.

Few areas where there were discrepancies across the population of psychosis and cirrhosis are as follows:

Alcohol interventions

- Women with alcoholic cirrhosis were more likely than men to receive interventions. However, for alcoholic psychosis the likelihood for men and women to receive interventions was similar.

Alcohol-attributable morbidities

- The strongest association with later development of cirrhosis was found among patients who had presented previously with injuries, seizures or digestive diseases. For alcoholic psychosis, injuries and epileptic seizures, were the strongest predictors.

Timing of alcohol-attributable disease burden

- With respect to timing, in patients with psychosis, morbidities appeared to be less common in the periods farthest away from diagnosis than in the year of diagnosis. However in alcoholic cirrhosis, very strong associations can be seen for both intentional and unintentional injuries and epilepsy even as far as 10 years before diagnosis.

8.2 Thesis strengths

There are certain strengths of this thesis that are worth summarising though they have been discussed in more detail within the study chapters. Firstly, the studies presented here represent the largest and most contemporary retrospective studies of healthcare utilisation and alcohol use interventions in people with alcoholic cirrhosis and psychosis. With 2,479 alcoholic cirrhosis cases, these studies are almost thirty times as big as the previous largest study (Table 3.1). For alcoholic psychosis, this is novel, as there have been no previous studies looking at healthcare utilisation in patients with the disease in relation to prevention opportunities.

The large amount of statistical power in the thesis studies provided the opportunity like never before to derive precise estimates of health care utilisation in these important group of people with chronic alcoholism. It also allowed further detailed

analysis of results including age and sex stratification in situations where significant interactions were found.

By frequency matching the cases to controls by age and general practice, two important things have been achieved. First, some biases due to unseen practice level factors which cannot be adjusted for statistically have been minimised. Secondly, as age and general practice are strong determinants of healthcare utilisation, selecting a control population with similar characteristics, provides the assurance that increases in healthcare utilisation rates in cases, are not just driven by age but by the alcoholic disorders or other related morbidities which led to the diagnosis of the alcoholic disorders.

This thesis has used general practice and hospital data which have national coverage; hence it is reasonable to assume that the thesis findings are representative of the true clinical activity of people with alcoholic cirrhosis and psychosis in the English population. It could be argued that only data from CPRD-HES linked practices were used and that therefore the representativeness of the study population has been affected. While this thesis has not specifically set out to investigate this, as previously mentioned, two recent studies have shown that people in HES-linked practices are not substantially different from non-linked practices in terms of demography providing the confidence that the study cases are indeed reasonably representative (157,176).

The method used to define the population of alcoholic cirrhosis has been previously validated in both datasets, and this gives the assurance that people identified as having the disease have been correctly identified.

Finally, previous studies have shown that using either primary or secondary care datasets independently, substantially underestimates the number of people with alcoholic cirrhosis. This is mainly because lapses in communication between primary and secondary care mean that a diagnosis made in secondary care for instance may not

be communicated to primary care as it should. By using the CPRD-HES linked data, this issue has been avoided.

8.3 Issues identified

Despite the above strengths there are a number of issues which were identified in this thesis.

First is that of potential information bias, a common problem with studies that make use of routinely collected datasets. As acknowledged in chapters 4 and 6, it is possible that there are cases when brief advice for alcohol use is given to patients but not systemically recorded in the database. Additionally there is also the possibility that drinking status may not be recorded for people who do not show any obvious signs of alcohol problems. Although it is not clear the extent to which under-recording occurs, it is likely that the true proportion of people who may have received interventions is greater than the 20% seen in these data.

Inconsistencies were also noted in patient alcohol records; for example, there were cases of alcoholic cirrhosis that had a status of “never-drinker”. This reiterates the widely accepted notion that people are often insincere about their levels of alcohol consumption or underestimate the total units of alcohol they consume and that practitioner records consequently reflect this inaccuracy in reporting.

An additional complexity of primary care data is the use of non-specific codes for coding of clinical events. In the course of this thesis, some alcohol related codes were identified which do not specify volume or frequency of drinking and were therefore incompletely sensitive to distinguishing between harmful and hazardous drinking. This requires important consideration as it could have led to differential misclassification of drinking status whereby some patients will be assigned to a lower drinking category than is correct.

Through several methodological approaches, some of these potential biases were minimised. For example, by defining drinking status as the highest level of consumption in the period before diagnosis using a combination of absolute unit consumption data and diagnostic Read codes, the potential impact of misclassification bias was minimized to an extent. Additionally, by reporting relative rates of interventions, meaningful results on clinical practice can still be deduced amidst the likelihood that absolute rates represent underestimated Figures of true alcohol preventive work.

In contrast to using a database approach for this thesis, using a clinical study where alcohol use assessment and the delivery of interventions could have been monitored, would have been extremely expensive, time consuming, and would have resulted in a much smaller and less representative population. It would have also not been able to provide access to the vast clinical history of patients that was available in CPRD and HES to inform the studies that assessed patterns of healthcare utilisation (The CPRD has since 1987 prospectively recorded data for patients included within the database).

Other limitations

Other general limitations, as acknowledged in section 3, include the fact that unlike for alcoholic cirrhosis, the method used to define the population of alcoholic psychosis has not been previously validated. As described in section 3.2, a validation attempt which involved looking for supporting evidence in primary care that could substantiate the diagnoses made in secondary care, and looking in secondary care for evidence that could substantiate those diagnoses made in primary care, was made. The general assumption behind this was that any patient having supporting evidence of their diagnosis in the alternate dataset (e.g. prescription for anti-psychotic medication in

primary care for those diagnosed in secondary care) had been correctly identified. The results showed that 89% of patients with alcoholic psychosis selected for this thesis have some supportive evidence in the alternate dataset. It is acknowledged that this is not, of course, an entirely robust method of validation; however it provides a certain degree of assurance about the reliability of the code lists and case selection method. An alternative and more sensitive way to have validated the diagnosis as highlighted in chapter 6 would have been to directly obtain and examine paper records from GP's for any confirmatory information relating to the electronic diagnosis of alcoholic psychosis. Alternatively using free text records from GPs may have provided more information. However, both services come with a high financial cost (for example, the paper record validation service costs at least £100 per subject) and due to limited resources, it was not possible to do this within this thesis. Given that there are specific diagnostic criteria for diagnosing alcoholic psychosis, it is reasonable to assume that it is unlikely that general practitioners have recorded this diagnosis in error for patients. As for the 11% of patients without any supporting evidence, most of whom were diagnosed in hospital; the likely explanation is that, as expected, not all patients who present for the first time in hospital with psychosis would have previously attended primary care.

Also worth noting with relevance to the morbidity studies, is a potential issue of reverse causality and the inability of the thesis to confirm the specificity of the association between alcohol use and the partially alcohol attributable comorbidities that were assessed. Although these comorbidities are widely reported to be associated with alcoholism, it is crucial to emphasize that this thesis did not assess the timing between the commencement of heavy drinking in patients and the occurrence of each morbidity. Even if this was planned, it may not have been feasible to ascertain temporal association for some diseases with long subclinical periods like diabetes,

where it is only possible to determine the “diagnosis date” of the disease rather than the date of disease development.

Finally, because some of the morbidities studied are not very common, there are some instances where the analyses are underpowered. By presenting confidence intervals, it has been made clear when this has occurred. On the whole, this has not occurred for more than one ICD-10 disease category, hence the potential impact should not be large.

8.4 Implications for clinical practice

There are a number of implications for clinical practice and alcohol control policies that can be drawn from these findings.

i. Potential opportunities to improve efforts at alcohol misuse prevention

The consistent finding of high rates of health service utilisation among cirrhosis and psychosis cases during the pre-diagnosis period suggests that there are opportunities which could be used to identify more high risk drinkers and provide more interventions for people drinking at levels which put their health at risk. Based on the data, the rates of both primary care consultations and hospital admissions was significantly higher in those who subsequently developed the severe alcoholic diseases, with the difference being up to 4 times higher in some situations. An analysis of consulting patterns over time, even further showed this high healthcare use to be present even up to 7 to 8 years pre-diagnosis of cirrhosis and psychosis. There is currently little information on whether these opportunities for intervening exist for heavy drinking populations despite early identification being recommended as a national strategy, so this is an important addition.

ii. Practitioners may be more aware of their role in preventing alcohol harm

Secondly, as high as 80% of patients had their alcohol use habit recorded during the pre-diagnosis period. Previous studies have shown as low as 27% of primary care patients with correct records of alcohol consumption(219). While changes in recording over time have not been directly assessed in the thesis, the results showing over 60% of controls and over 80% of cases with useable alcohol records is certainly higher than what has been previously reported and might imply that practitioners in the UK may be more aware, than has been previously reported, of their role in helping to reduce the harmful effects of risky drinking within the context of primary care.

iii. The need for more efforts to encourage the wider implementation of alcohol interventions

Perhaps this is the most important implication of the findings of this thesis. The studies in this thesis found that many patients did not have any evidence of an offered an intervention. In interpreting these findings, the nature of the data used should be considered. It is possible that there are situations where physicians intervened for heavy drinking but did not record them within the patient's electronic healthcare records. This would suggest that the estimates identified in my thesis are lower than the real extent of implementation. Nevertheless, this does not alter the fact that despite efforts to encourage brief interventions both in the UK and internationally, the extent to which people receive advice about their drinking is low(115,144,184). Given the detrimental effects of excessive alcohol consumption, the implication of this is that more effort needs to be made to monitor drinking habits and deliver interventions to people with known drinking problems.

As acknowledged earlier, there are several interrelated factors which may account for suboptimal use of interventions, or gaps in recording practices. They include time priorities, lack of workplace support, poor financial reimbursement, fears about the effectiveness of interventions and feelings of inadequacy to deliver interventions(148). In addition to these organisational and attitudinal barriers, there may also be other barriers to implementation. For instance a study on nurses suggested that nurses who used alcohol themselves were more relaxed about providing advice on drinking , to suggest that attitudes towards of healthcare staff towards drinking could interfere with brief intervention implementation(151).

To some extent, some of these barriers can be overcome and this has been the focus of on-going local and international research. An important first response to these barriers would presumably involve educating practitioners particularly around the value of intervening early for alcohol misuse and the limitations to continuity of care when intervention activities are not documented. In Sweden, a government national project known as the National Brief Intervention Project was started in 2004 with the aim of encouraging wide spread implementation of screening and brief interventions. The programme provided training and support for 3000 healthcare staff (2000 nurses and 1000 GPs) to carry out screening and brief interventions. In a recent evaluation of the programme, it was shown that this training effort led to an increase in intervening activity among Finnish physicians, with the proportion of those carrying out interventions increasing from 59% to 79%. Though it is acknowledged that the current level of intervention in Finland is still lower than what is necessary to cause a population level reduction in alcohol related harm, the authors reported that an increasing trend in implementation is being seen. Such training programmes could be beneficial for countries like the UK where relatively less effort is being put towards

encouraging implementation. There are some previous research which have shown that training and support may only serve to increase screening and intervening rates among GPs who already feel committed in working with drinkers(187,208). Thus, the key point here may be a training programme that is provided for those practitioners who demonstrate commitment to addiction medicine.

Another important barrier to implementation that is widely cited in the UK is that of financial reimbursement. A logical response to this has been a debate about whether alcohol use screening should be included in the QOF, the comprehensive contract which incentivises General practitioners in the UK for meeting certain healthcare quality targets. Data from smoking cessation in the UK showed that introducing a QOF indicator that rewards recording of smoking status led to an increase in the recording of smoking habits and cessation advice in UK general practices (220). In 2008, a pilot QOF-extra scheme was introduced in 30 General practices in north-west London, whereby participating practices were incentivised to screen patients with mental health conditions and cardiovascular disease. Recent analysis of this scheme suggested that the QOF-extra scheme led to an increase in screening for alcohol misuse among all patients, and had a spill-over effect even in those not covered by the scheme. The proportion of patients with mental health conditions and cardiovascular disease being screened for heavy drinking was 65.7% after the QOF extra scheme compared to 4.8% prior to the scheme(221). This programme however ended in 2011 due to restricted funding. This encouraging evidence not only shows the potential of such a scheme, but also favours the suggestion that perhaps systematically rolling out a pay for performance initiative for alcohol misuse at a national level could be the next important step to improve how alcohol misuse is addressed within healthcare settings. Since the QOF currently only incentivises GPs when they screen for alcohol use in

specific groups of people (222), it is highly likely that introducing a more comprehensive QOF indicator that rewards practitioners for providing interventions for all individuals known to be heavy drinkers could substantially improve screening and intervention activity among practitioners (139).

At present there is the concern about whether the wider implementation of brief interventions would actually make a difference to alcohol related harm. It is therefore important to briefly re-evaluate the available evidence and principles behind the use of behavioural interventions.

Brief interventions are grounded in behavioural change techniques which recognise that, for an individual to change an existing behaviour there is an interaction between the individual's capability to change, motivation, and opportunity(223). Drawing on fairly recent novel work by Michie et al(224) where the content of brief interventions for alcohol were characterised, it was found that at least 42 of these behavioural change techniques which influence different aspects that motivate a behavioural change are employed in brief alcohol interventions. The most frequently used BCT was identified to be motivational counselling which has proved successful in modifying behavioural change in other lifestyle areas such as smoking(225), healthy eating, and exercise(224).

In terms of the exact potential effect of brief interventions, the first well-conducted trial of the effect of GP delivered brief interventions found that brief interventions led to a 43.7% reduction in the harmful drinking prevalence among the group receiving the intervention compared with 25.5% in the control group after a year of follow-up(226). Based on this result it has since been estimated that brief interventions by GPs at the national level could potentially lead to a reduction of excessive drinking in 250,000

men and 67,500 women each year. Other measures of effectiveness that have been reported for brief interventions include NNT, weekly alcohol reduction and reduction in mortality. The NNT for brief interventions is currently estimated at between 8 and 10, implying that for every 8 to 10 people who are offered brief advice on their drinking, one will go on to modify their drinking behaviour(130). As mentioned earlier, NNT in some sense underestimates the effectiveness of this intervention because even if patients do not respond initially, the intervention may initiate a movement along the stages of change as shown in the trans-theoretical model in figure 1-7(227). The NNT for alcohol interventions however compares favourably with the already established smoking cessation intervention which has a NNT of 20(132).

Given these results, healthcare workers should actually be encouraged to include brief alcohol screening and counselling in their normal routine practice.

iv. Possibility of identifying heavy drinkers using prompting systems attached to electronic health records

Finally, the analysis of comorbidities in individuals prior to the diagnosis of alcoholic cirrhosis and psychosis has highlighted potential pointers to those patients who may be at risk of alcohol related harm. Based on the thesis findings, people with alcoholic cirrhosis and psychosis were more likely to present to healthcare for digestive diseases, injuries and nervous system diseases. From an epidemiological perspective, these findings imply that if people who present with these conditions undergo a thorough alcohol use assessment it could be possible to identify at-risk drinkers who may benefit the most from targeted interventions.

One practical consideration of this however is that while these three conditions showed very strong risks of the later development of cirrhosis and psychosis, the

absolute number of people who presented with them are relatively fewer than those who presented with conditions with modest risks. This implies that although relying on these conditions may help to correctly identify those who are at risk, only a small proportion of heavy drinkers can be identified this way.

Ultimately, the major way to avoid this is if practitioners could at the very least focus on groups of patients who present with any alcohol related condition. This targeted screening is already recommended in the Alcohol harm Reduction strategy although it is not clear to what extent the uptake of this guidance is in primary and secondary care settings(5). Another alternative approach which would even capture a larger group of heavy drinkers is universal screening. The Public health PH24 guidance issued by NICE recommends this universal screening whereby NHS healthcare professionals are advised to screen for alcohol use in all patients where feasible(22). This has however met with substantial resistance, probably due to the increased workload it suggests.

As a starting point however, the information on comorbidities cited above can be explored in future, and in addition to other sociodemographic information, could be used to develop risk prediction algorithms. Such algorithms could then be incorporated within electronic records in such a way that patients who have a combination of risk factors that indicate potential heavy alcohol use would be flagged up to practitioners during consultations. Such risk prediction models and flagging systems have already been developed for several other conditions e.g. cancers; and is likely to be of great value to practitioners whose likelihood to identify at-risk drinkers may be constrained by time.

8.5 Implications for future research

There are a number of avenues that can be investigated following this thesis to further strengthen the prevention of alcohol use disorders.

8.5.1 Using patients with other alcohol related diseases to answer similar research questions

The results of this thesis have been based on people with two specific 100% alcohol-attributable diseases, alcoholic cirrhosis and psychosis. As described earlier, these diseases were chosen as they represent a heavy drinking population and a population with significant morbidity and mortality impact. It is however possible that there are other groups of heavy drinkers who may have comorbidity and consultation patterns that differ from what has been found in this thesis. Therefore future studies could replicate this work using people with other 100% alcohol-attributable diseases e.g. alcoholic hepatitis to ensure that if there are any other patterns not captured in this thesis, they are not being missed.

8.5.2 Additional data and methods

8.5.2.1 Use of free-text data

This thesis quantified the proportion of patients who had been screened for heavy drinking or provided with interventions using only information that was recorded within structured coded fields of electronic primary care records. There are several limitations to this which suggest that further research would be helpful.

First, within the CPRD, the structured data fields are supplemented with free text fields that provide clinicians with flexibility during data entry. In several studies practitioners have been found to record diagnostic and prescribing information within these free-text fields therefore it is likely that alcohol information may be recorded there as well (228). Though free-text records are obtained at a high cost, further research analysing such records would potentially help to give a more comprehensive insight to the extent of intervention activity that goes on unrecorded within primary care settings.

8.5.2.2 Mixed methods research

Secondly, there are several characteristics that may influence the recording of alcohol status or the recording of interventions in the general population which cannot be teased out of the data used for this thesis. These include GP characteristics such as gender, training and drinking status, or even practice characteristics namely staffing and location. More research can help understand the role that these factors may have played in the study results. Therefore mixed methods research which would employ focus groups to explore patient, practitioner and practice attributes may be beneficial as it would give more insights to why and for whom alcohol status and interventions are recorded in general practice.

8.5.3 Practice-level research

It was not feasible to assess variations in recording practises across practices and regions within the time available for this thesis. However it would be beneficial if further studies could identify those practices or regions with high levels of recording

and their characteristics, as they could then be used as the standard to inform best practice guidelines.

8.5.4 Potential for risk prediction modelling

Risk prediction tools are now being developed and used across general practice settings to identify people at high risk of diseases which are otherwise fatal if identified at an advanced stage. Several alcohol use disorders namely cirrhosis and psychosis fall within this category, but as there are currently no formal tools to predict those who may be at risk, further quantitative studies that can develop a model that predicts people at high risk of such alcohol use disorders may be beneficial.

Developing the risk prediction tool would involve incorporating all the potential morbidities that heavy drinkers are likely to present with prior to when they have a recognised severe alcoholic disease (as identified in this thesis), with other patient demographic characteristics such as age, gender, BMI and Socio-economic status. The developed tool could be integrated in electronic primary care data as has been the case for cancer and several cardiovascular diseases, and then used to identify those patients that will benefit most from targeted interventions.

8.5.5 Economic modelling studies

Although the overall cost of alcohol related harm to the UK has been estimated, estimating the costs associated with high risk individuals who are not identified in a timely manner may serve a few purposes. First, it could be used to make the case against the delay of legislations or policies that can positively influence the level at which practitioners implement interventions. Secondly, it could also be used as a starting point for estimating future health care needs for planning purposes. As this

thesis has already produced comprehensive estimates of health care utilisation among these high risk patients in comparison to the general population, these could be used as the basis for such economic modelling work.

8.5.6 Other outcomes

Timing

To fully capitalise on the study data, modelling the timing of events is required. Timing of interventions was not a principal focus of this thesis, therefore further studies which give more consideration to the timing of screening, and intervention in relation to the timing of the first record of heavy drinking or the timing of diagnosis, are needed to get a better picture how much earlier we can be identifying people at high risk of alcohol problems.

Effect of brief interventions

It was outside the scope of this thesis to assess whether there were different outcomes in patients who received interventions versus those who did not. However it may be interesting to see whether survival or prognosis after disease diagnosis is different in both groups. This information would be useful to clinicians as well as those who advocate the implementation of brief alcohol interventions.

8.5.7 Conclusions

Given the increase in alcohol related harm in the UK, there is a justifiable focus on the topic area that has been assessed in this thesis. The main conclusion of this thesis is that there are opportunities to implement evidence-based interventions for heavy drinkers, however, many heavy drinkers are not provided with these evidence-based interventions. This gap in intervention delivery has potential consequences for public health and implies that more national efforts to address potential factors that act as disincentives to preventive work are needed. Additionally, it also implies that practitioners need to do more to achieve the widespread implementation of screening and brief interventions that presupposes any public health benefit.

References

1. Rehm J, Room R, Monteiro M, Gmel G, Graham K, Rehn N. Comparative quantification of health Risks-Alcohol Use.
2. World Health Organisation. WHO Statistical Classification of Diseases and Related Health Problems (ICD) 10th revision. WHO,Geneva.; 1992.
3. World Health Organisation. The ICD-10 Classification of Mental and Behavioural Disorders Diagnostic criteria for research. WHO,Geneva.; 1992.
4. Rehm J, Baliunas D, Borges GLG, Graham K, Irving H, Kehoe T, et al. The relation between different dimensions of alcohol consumption and burden of disease: an overview. *Addiction*. 2010;105(5):817–43.
5. The Cabinet Office. Alcohol Harm Reduction Strategy for England. 2004.
6. Taylor B, Irving HM, Kanteres F, Room R, Borges G, Cherpitel C, et al. The more you drink, the harder you fall: A systematic review and meta-analysis of how acute alcohol consumption and injury or collision risk increase together. *Drug Alcohol Depend*. 2010 Jul 1;110(1–2):108–16.
7. World Health Organisation. Global status report on alcohol and health. 2011.
8. The Royal College of Physicians. A Great and Growing Evil: the medical consequences of alcohol abuse. 1987.
9. World Health Organisation. Global status report: alcohol and young people. [Internet]. WHO,Geneva.; 2001 [cited 2013 Apr 7]. Available from: http://whqlibdoc.who.int/hq/2001/who_msd_msb_01.1.pdf
10. British Medical Association. Fetal alcohol spectrum disorders: A guide for healthcare professionals. 2007.
11. Office for National Statistics. Crime in England and Wales, Year Ending June 2014. ONS; 2014.
12. Office for National Statistics. Crime in England and Wales, Year Ending 2012. ONS; 2012.
13. Rehm J, Zatonksi W, Taylor B, Anderson P. Epidemiology and alcohol policy in Europe. *Addiction*. 2011 Mar 1;106:11–9.

14. Laslett A-M, Room R, Dietze P, Ferris J. Alcohol's involvement in recurrent child abuse and neglect cases. *Addiction*. 2012 Oct 1;107(10):1786–93.
15. Aicken CRH, Nardone A, Mercer CH. Alcohol misuse, sexual risk behaviour and adverse sexual health outcomes: evidence from Britain's national probability sexual behaviour surveys. *J Public Health*. 2011 Jun 1;33(2):262–71.
16. Anderson P, Moller L, Galea G. Alcohol in the European Union. Consumption, harm and policy approaches. WHO regional office for Europe; 2012.
17. Rehm J. Interventions for alcohol dependence in Europe: a missed opportunity to improve public health. 2012.
18. Roerecke M, Rehm J. The cardioprotective association of average alcohol consumption and ischaemic heart disease: a systematic review and meta-analysis. *Addict Abingdon Engl*. 2012 Jul;107(7):1246–60.
19. Rehm J, Sempos CT. Alcohol consumption and all-cause mortality. *Addict Abingdon Engl*. 1995 Apr;90(4):471–80.
20. Shaper AG. Alcohol and mortality: a review of prospective studies. *Br J Addict*. 1990 Jul;85(7):837–47; discussion 849–61.
21. Shaper AG, Wannamethee SG. The J-shaped curve and changes in drinking habit. *Novartis Found Symp*. 1998;216:173–88; discussion 188–92.
22. NICE. Alcohol-use disorders:preventing harmful drinking. NICE guidelines PH24. National Institute for Health and Clinical Excellence; 2010.
23. Health and Social Care Information Centre. Statistics on Alcohol: England, 2012. 2012.
24. Room R. Drinking patterns in large U.S. cities. A comparison of San Francisco and national samples. *Q J Stud Alcohol*. 1972; Supple 6:23-57.
25. Scottish Intercollegiate Guidelines Network (SIGN). The management of harmful drinking and alcohol dependence in primary care. 2004.
26. House of Commons Science and Technology Committee. Alcohol guidelines: Eleventh Report of session 2010-12. House of Commons; 2012.
27. World Health Organisation. Global status report on alcohol and health. WHO,Geneva.; 2014.
28. Rehm J, Rehn N, Room R, Monteiro M, Gmel G, Jernigan D, et al. The Global Distribution of Average Volume of Alcohol Consumption and Patterns of Drinking. *Eur Addict Res*. 2003;9(4):147–56.

29. Macdonald S, Green A, Brubacher J, Cherpitel C, Stockwell C, Zeisser C. Alcohol consumption and injury. Alcohol: science, policy and public health. Oxford: Oxford University Press, In. Oxford; 2013.
30. World Health Organisation. Global Status Report on Alcohol 2004. Department of Mental Health and Substance Abuse; 2004.
31. Rehm J, Room R, Graham K, Monteiro M, Gmel G, Sempos CT. The relationship of average volume of alcohol consumption and patterns of drinking to burden of disease: an overview. Addiction. 2003 Sep 1;98(9):1209–28.
32. OECD. Health at a glance: Europe 2012. Paris: Organisation for Economic Co-operation and Development; 2012.
33. WHO. Global Information system on Alcohol and Health [Internet]. 2015 [cited 2013 Jul 20]. Available from: <http://www.who.int/gho/alcohol/en/>
34. The Lancet. Calling time on young people's alcohol consumption. The Lancet. 371(9616):871.
35. Office for National Statistics(ONS). Opinions and Lifestyle Survey(OPN) [Internet]. [Assessed 10 Aug 2015]. Available from: <http://www.ons.gov.uk/ons/rel/ghs/opinions-and-lifestyle-survey/index.html>
36. Health and Social Care Information Centre. Health Survey for England; Health, social care and lifestyles. [Internet]. [Assessed 10 July 2014] Available from: <http://www.hscic.gov.uk/healthsurveyengland>
37. World Health Organisation. International guide for monitoring alcohol consumption and related harm. Department of Mental Health and Substance Abuse; 2000.
38. Health and Social Care Information Centre. Statistics on Alcohol England, 2014. 2014.
39. Lesley Smith, Foxtrot D. Drinking in the UK: An exploration of trends. 2009.
40. NHS. Adult Psychiatric Morbidity in England, 2007: results of a household survey. 2009;
41. Office for National Statistics. Statistical bulletin: Drinking habits amongst adults,2013 [Internet]. 2015. Available from: <http://www.ons.gov.uk/ons/rel/ghs/opinions-and-lifestyle-survey/adult-drinking-habits-in-great-britain--2013/index.html>
42. Institute of Alcohol Studies. Young people and alcohol factsheet. Institute of Alcohol studies; 2013.

43. Office for National Statistics. Statistics on Alcohol: England, 2013. 2013.
44. Office for National Statistics. Statistical Bulletin: Alcohol-related deaths in the United Kingdom, registered in 2012. Office for National Statistics 2014;
45. Centers for Disease Control and Prevention. Behavioral Risk Factor Surveillance System prevalence data. Atlanta,GA:CDC;
46. Department of Health. Annual report of the Chief Medical Officer on the State of the Public's health [Internet]. Department of Health; 2014. Available from:
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/298297/cmo-report-2012.pdf
47. Jones L, Bates G, McCoy E, Bellis MA. Relationship between alcohol-attributable disease and socioeconomic status, and the role of alcohol consumption in this relationship: a systematic review and meta-analysis. BMC Public Health. 2015;15:400. doi: 10.1186/s12889-015-1720-7.
48. Department of Health. The Annual Report of the Chief Medical Officer of the Department of Health 2001. Department of Health; 2001.
49. Department of health. The Annual Report of the Chief Medical Officer 2011: On the State of the public's health. 2012.
50. The Cabinet Office. Alcohol misuse: How much does it cost? 2003.
51. Scarborough P, Bhatnagar P, Wickramasinghe KK, Allender S, Foster C, Rayner M. The economic burden of ill health due to diet, physical inactivity, smoking, alcohol and obesity in the UK: an update to 2006–07 NHS costs. J Public Health. 2011 Dec 1;33(4):527–35.
52. Alcohol Concern. Statistics on Alcohol. Alcohol concern; 2015.
53. Lister G. Evaluating social marketing for health: The need for consensus, Proceedings of the National Social Marketing Centre. 2007.
54. Sherlock S, Dooley J. Hepatic Cirrhosis. In: Diseases of the Liver and Biliary System [Internet]. Blackwell Science Ltd; 2001. p. 365–80. Available from: <http://dx.doi.org/10.1002/9780470986820.ch21>
55. Schuppan D, Afdhal NH. Liver cirrhosis. The Lancet. 8;371(9615):838–51.
56. Benyon RC, Iredale JP. Is liver fibrosis reversible? Gut. 2000 Apr 1;46(4):443–6.
57. Leon DA, McCambridge J. Liver cirrhosis mortality rates in Britain from 1950 to 2002: an analysis of routine data. The Lancet. 7;367(9504):52–6.

58. Fleming KM, Aithal GP, Solaymani-Dodaran M, Card TR, West J. Incidence and prevalence of cirrhosis in the United Kingdom, 1992–2001: A general population-based study. *J Hepatol.* 11;49(5):732–8.
59. Ratib S, West J, Crooks CJ, Fleming KM. Diagnosis of Liver Cirrhosis in England, a Cohort Study, 1998-2009: A Comparison with Cancer. *Am J Gastroenterol.* 2014 Feb;109(2):190–8.
60. NHS. Deaths from Liver disease: Implications for end of life care in England. 2012.
61. Gramenzi A, Caputo F, Biselli M, Kuria F, Loggi E, Bernardi M. Review article: alcoholic liver disease – pathophysiological aspects and risk factors. *Aliment Pharmacol Ther.* 2006;24(8):1151–61.
62. Kamper-Jørgensen M, Grønbaek M, Tolstrup J, Becker U. Alcohol and cirrhosis: dose–response or threshold effect? *J Hepatol.* 2004;41(1):25–30.
63. Rehm Jür, Taylor B, Mohapatra S, Irving H, Baliunas D, Patra J, et al. Alcohol as a risk factor for liver cirrhosis: A systematic review and meta-analysis. *Drug Alcohol Rev.* 2010;29(4):437–45.
64. Bellentani S, Saccoccio G, Costa G, Tiribelli C, Manenti F, Sodde M, et al. Drinking habits as cofactors of risk for alcohol induced liver damage. *Gut.* 1997 Dec 1;41(6):845–50.
65. Savolainen VT, Liesto K, Mannikko A, Penttilä A, Karhunen PJ. Alcohol consumption and alcoholic liver disease: Evidence of a threshold level of effects of ethanol. *Alcohol Clin Exp Res.* 1993;17(5):1112–7.
66. Becker U, Deis A, Sorensen T, Gronbaek M, Borch-Johnsen K, Muller C, et al. Prediction of Risk of Liver Disease by Alcohol Intake, Sex, and Age: A Prospective Population Study. *Hepatology.* 1996;23(5):1025–9.
67. Askgaard G, Grønbaek M, Kjær MS, Tjønneland A, Tolstrup JS. Alcohol drinking pattern and risk of alcoholic liver cirrhosis: A prospective cohort study. *J Hepatol.* 2015;62(5):1061–7.
68. Kevin Walsh, Graeme Alexander. Alcoholic liver disease. *Postgrad Med J.* 2000;76:280–6.
69. Peter Jepsen, Hendrik Vilstrup, Per Kragh Andersen, Timothy L. Lash, Sørensen HT. Comorbidity and survival of Danish cirrhosis patients: A nationwide population-based cohort study. *Hepatology.* 2008;48(1):214–20.
70. Fleming KM, Aithal GP, Card TR, West J. All-cause mortality in people with cirrhosis compared with the general population: a population-based cohort study. *Liver Int.* 2012;32(1):79–84.

71. Mukerji AN, Patel V, Jain A. Improving Survival in Decompensated Cirrhosis. *Int J Hepatol*. 2012;2012:14.
72. Verrill C, Markham H, Templeton A, Carr NJ, Sheron N. Alcohol-related cirrhosis—early abstinence is a key factor in prognosis, even in the most severe cases. *Addiction*. 2009;104(5):768–74.
73. Sorensen HT, Thulstrup AM, Mellekjaer L, Jepsen P, Christensen E, Olsen JH, et al. Long-term survival and cause-specific mortality in patients with cirrhosis of the liver: a nationwide cohort study in Denmark. *J Clin Epidemiol*. 2003 Jan;56(1).
74. Ratib S, Fleming KM, Crooks CJ, Walker AJ, West J. Causes of Death in People with Liver Cirrhosis in England Compared with the General Population: A Population-Based Cohort Study. *Am J Gastroenterol*. 2015 Aug;110(8):1149–58.
75. Saunders JB, Walters J, Davies P, Paton A. A 20 year prospective study of cirrhosis. *Br Med J*. 1981;282(263-282).
76. Borowsky SA, Strome S, Lott E. Continued heavy drinking and survival in alcoholic cirrhotics. *Gastroenterology*. 1981 Jun;80(6):1405–9.
77. Garceau AJ. The Natural History of Cirrhosis. *N Engl J Med*. 1964 Dec 3;271(23):1173–9.
78. Pessione F, Ramond MJ, Peters L, Pham BN, Batel P, Rueff B, et al. Five-year survival predictive factors in patients with excessive alcohol intake and cirrhosis. Effect of alcoholic hepatitis, smoking and abstinence. *Liver Int Off J Int Assoc Study Liver*. 2003 Feb;23(1).
79. Diehl AM. Alcoholic liver disease: Natural history. *Liver Transpl Surg*. 1997 May 1;3(3):206–11.
80. Verrill C, Smith S, Sheron N. Are the opportunities to prevent alcohol related liver deaths in the UK in primary or secondary care? A retrospective clinical review and prospective interview study. *Subst Abuse Treat Prev Policy*. 2006 Jun 15;1(1):1–5.
81. Morris M, Johnson D, Morrison DS. Opportunities for prevention of alcohol-related death in primary care: results from a population-based cross-sectional study. *Alcohol Fayettev N*. 2012 Nov;46(7):703–7.
82. Puri B. Medication- and substance-induced disorders. *Textbook of Clinical Neuropsychiatry and Behavioral Neuroscience*. London, United Kingdom: Hodder Arnold; 2012.

83. Jordaan GP, Warwick JM, Nel DG, Hewlett R, Emsley R. Alcohol-induced psychotic disorder: brain perfusion and psychopathology--before and after anti-psychotic treatment. *Metab Brain Dis*. 2012 Mar;27(1):67–77.
84. Perälä J, Kuoppasalmi K, Pirkola S, Härkänen T, Saarni S, Tuulio-Henriksson A, et al. Alcohol-induced psychotic disorder and delirium in the general population. *Br J Psychiatry*. 2010 Sep 1;197(3):200–6.
85. Jordaan GP, Emsley R. Alcohol-induced psychotic disorder: a review. *Metab Brain Dis*. 2014 Jun;29(2):231–43.
86. Glass IB. Alcoholic hallucinosis: a psychiatric enigma--2. Follow-up studies. *Br J Addict*. 1989 Feb;84(2):151–64.
87. Jones L, Bellis M. Updating England-Specific Alcohol-attributable Fractions. Centre for Public health: Liverpool John Moore University.
88. Bertelsen M, Jeppesen P, Petersen L, Thorup A, Øhlenschlaeger J, Quach PL, et al. Suicidal behaviour and mortality in first-episode psychosis: the OPUS trial. *Br J Psychiatry*. 2007 Nov 30;191(51):s140–6.
89. George S, Chin CN. A 3 year case study of alcohol related psychotic disorders at Hospital Seremban. *Med J Malaysia*. 1998 Sep;53(3):223–6.
90. Soyka M. [Alcohol-induced hallucinosis. Clinical aspects, pathophysiology and therapy]. *Nervenarzt*. 1996 Nov;67(11):891–5.
91. Yang Z. Alcohol related psychosis [Internet]. Alcohol-related psychosis. [cited 2015 Jan 20]. Available from: <http://emedicine.medscape.com/article/289848-overview>.
92. Soyka M. Pharmacological treatment of alcohol hallucinosis. *Alcohol Alcohol Oxf Oxf*. 2008 Dec;43(6):719–20; author reply 720.
93. Alcohol Health Alliance UK. Health First: an evidence-based alcohol strategy for the UK. 2013.
94. Department of Health. Safe. Sensible. Social. The next steps in the national alcohol strategy. 2007.
95. Royal College of Physicians of London. ALCOHOL – can the NHS afford it? 2001.
96. Wagenaar AC, Salois MJ, Komro KA. Effects of beverage alcohol price and tax levels on drinking: a meta-analysis of 1003 estimates from 112 studies. *Addiction*. 2009 Feb 1;104(2):179–90.
97. Stockwell T, Chikritzhs T, Hendrie D, Fordham R, Ying F, Phillips M, et al. The public health and safety benefits of the Northern Territory's Living with Alcohol programme. *Drug Alcohol Rev*. 2001 Jun 1;20(2):167–80.

98. Farrell S, Manning WG, Finch MD. Alcohol dependence and the price of alcoholic beverages. *J Health Econ.* 2003 Jan;22(1):117–47.
99. Holmes J, Meng Y, Meier PS, Brennan A, Angus C, Campbell-Burton A, et al. Effects of minimum unit pricing for alcohol on different income and socioeconomic groups: a modelling study. *The Lancet.* 10;383(9929):1655–64.
100. Woodhouse J. Mandatory Conditions for the sale of alcohol. House of Commons; 2015.
101. Alcohol insight. The effect of alcohol advertising and marketing on drinking behaviour in young people: a systematic review of published longitudinal studies. 2007.
102. UK Government. The Government’s Alcohol Strategy. 2012.
103. Snyder LB, Milici F, Slater M, Sun H, Strizhakova Y. Effects of alcohol advertising exposure on drinking among youth. *Arch Pediatr Adolesc Med.* 2006 Jan 1;160(1):18–24.
104. Foxcroft DR, Tsertsvadze A. Universal school-based prevention programs for alcohol misuse in young people. *Cochrane Database Syst Rev.* 2011;(5):CD009113.
105. Foxcroft DR, Tsertsvadze A. Universal multi-component prevention programs for alcohol misuse in young people. *Cochrane Database Syst Rev.* 2011;(9):CD009307.
106. World Health Organisation. Problems related to alcohol consumption, Report of a WHO Expert Committee. Technical Report Series 650. Geneva, WHO.; 1980.
107. Babor TF, Grant M, eds. Project on Identification and Management of Alcohol-Related Problems. Report on phase II: a randomized clinical trial of brief interventions in primary health care. Geneva World Health Organ. 1992;
108. Babor T, Higgins-Biddle J. Brief intervention for hazardous and harmful drinking: A manual for use in primary care. [Internet]. World Health Organisation; 2001. Available from: http://whqlibdoc.who.int/hq/2001/who_msd_msb_01.6b.pdf
109. Wutzke SE, Shiell A, Gomel MK, Conigrave KM. Cost effectiveness of brief interventions for reducing alcohol consumption. *Soc Sci Med.* 2001 Mar;52(6):863–70.
110. Purshouse RC, Brennan A, Rafia R, Latimer NR, Archer RJ, Angus CR, et al. Modelling the Cost-Effectiveness of Alcohol Screening and Brief

Interventions in Primary Care in England. *Alcohol Alcohol*. 2013 Feb 13;48(2):180–8.

111. Tariq L, van den Berg M, Hoogenveen RT, van Baal PHM. Cost-effectiveness of an opportunistic screening programme and brief intervention for excessive alcohol use in primary care. *PloS One*. 2009;4(5).
112. Fleming MF. Screening and brief intervention in primary care settings. *Alcohol Res Health*. 2004;28(2):57–62.
113. Fleming M, Manwell L. Brief Intervention in Primary Care settings: A primary Treatment Method for At-Risk, Problem and Dependent drinkers. *Alcohol Res Health*. 1999;23(2):128–37.
114. NICE. Services for the identification and treatment of hazardous drinking, harmful drinking and alcohol dependence in children, young people and adults. NICE commissioning guides CMG38. 2011.
115. Nilsen P, Kaner E, Babor T. Brief intervention, three decades on. *Nord Stud Alcohol Drugs*. 2008;25(6):453–67.
116. Sullivan LE, Tetrault JM, Braithwaite RS, Turner BJ, Fiellin DA. A Meta-analysis of the Efficacy of Nonphysician Brief Interventions for Unhealthy Alcohol Use: Implications for the Patient-Centered Medical Home. *Am J Addict*. 2011 Jul 1;20(4):343–56.
117. NICE. Alcohol use disorders: preventing the development of hazardous and harmful drinking. UK; 2010.
118. Saunders JB, Aasland OG, Babor TF, DE LA Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption-II. *Addiction*. 1993 Jun 1;88(6):791–804.
119. Hodgson R, Alwyn T, John B, Thom B, Smith A. The fast alcohol screening test. *Alcohol Alcohol*. 2002 Jan 1;37(1):61–6.
120. Mackenzie DM, Langa A, Brown TM. Identifying hazardous or harmful alcohol use in medical admissions: a comparison of audit, cage and brief mast. *Alcohol Alcohol*. 1996 Nov 1;31(6):591–9.
121. Bataille V, Ruidavets J-B, Arveiler D, Amouyel P, Ducimetière P, Perret B, et al. Joint use of clinical parameters, biological markers and cage questionnaire for the identification of heavy drinkers in a large population-based sample. *Alcohol Alcohol*. 2003 Mar 1;38(2):121–7.
122. Bush K, Kivlahan DR, McDonnell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project

- (ACQUIP). Alcohol Use Disorders Identification Test. *Arch Intern Med*. 1998 Sep 14;158(16):1789–95.
123. Lavoie D. Alcohol identification and brief advice in England: A major plank in alcohol harm reduction policy. *Drug Alcohol Rev*. 2010 Nov 1;29(6):608–11.
124. Winett RA. A framework for health promotion and disease prevention programs. *Am Psychol*. 1995 May;50(5):341–50.
125. Kaner E, Bland M, Cassidy P, Coulton S, Dale V, Deluca P, et al. Effectiveness of screening and brief alcohol intervention in primary care (SIPS trial): pragmatic cluster randomised controlled trial. *BMJ*. 2013 Jan 9;346.
126. Whitlock EP, Polen MR, Green CA, Orleans T, Klein J. Behavioral Counseling Interventions in Primary Care To Reduce Risky/Harmful Alcohol Use by Adults: A Summary of the Evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2004;140(7):557–68.
127. Wilk AI, Jensen NM, Havighurst TC. Meta-analysis of Randomized Control Trials Addressing Brief Interventions in Heavy Alcohol Drinkers. *J Gen Intern Med*. 1997;12(5):274–83.
128. Kaner EFS, Dickinson HO, Beyer F, Pienaar E, Schlesinger C, Campbell F, et al. The effectiveness of brief alcohol interventions in primary care settings: a systematic review. *Drug Alcohol Rev*. 2009 May;28(3):301–23.
129. Jonas DE, Garbutt JC, Amick HR, Brown JM, Brownley KA, Council CL, et al. Behavioral Counseling After Screening for Alcohol Misuse in Primary Care: A Systematic Review and Meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2012 Nov 6;157(9):645–54.
130. Ballesteros J, Duffy JC, Querejeta I, Arino J, Gonzalez-Pinto A. Efficacy of brief interventions for hazardous drinkers in primary care: systematic review and meta-analyses. *Alcohol Clin Exp Res*. 2004 Apr;28(4):608–18.
131. Bertholet N, Daeppen J-B, Wietlisbach V, Fleming M, Burnand B. Reduction of alcohol consumption by brief alcohol intervention in primary care: systematic review and meta-analysis. *Arch Intern Med*. 2005 May 9;165(9):986–95.
132. Silagy C, Stead LF. Physician advice for smoking cessation. *Cochrane Database Syst Rev*. 2001;(2):CD000165.
133. McQueen J, Howe T, Allan L, Mains D, Hardy V. Brief interventions for heavy alcohol users admitted to general hospital wards. *Cochrane Database Syst Rev* [Internet]. 2011;(8). Available from: 10.1002/14651858.CD005191.pub3

134. Gentilello LM, Rivara FP, Donovan DM, Jurkovich GJ, Daranciang E, Dunn CW, et al. Alcohol interventions in a trauma center as a means of reducing the risk of injury recurrence. *Ann Surg.* 1999 Oct;230(4):473–80; discussion 480–3.
135. Crawford MJ, Patton R, Touquet R, Drummond C, Byford S, Barrett B, et al. Screening and referral for brief intervention of alcohol-misusing patients in an emergency department: a pragmatic randomised controlled trial. *Lancet Lond Engl.* 2004 Oct 9;364(9442):1334–9.
136. National Audit Office. Reducing Alcohol Harm: health services in England for alcohol misuse. 2008.
137. BMA & NHS Employers. Clinical Directed Enhanced Services (DES) Guidance for GMS Contract 2008/09. London: BMA & NHS Employers; 2008.
138. The Information Centre. The Quality and Outcomes Framework [Internet]. 2012. Available from: <http://www.ic.nhs.uk/statistics-and-data-collections/audits-and-performance/the-quality-and-outcomes-framework>
139. Public Health England. NHS Health Check competence framework. Public Health England; 2014.
140. Hutchings D, Cassidy P, Dallolio E, Pearson P, Heather N, Kaner EFS. Implementing screening and brief alcohol interventions in primary care: views from both sides of the consultation. *Prim Health Care Res Dev.* 2006;7:221–9.
141. Cheeta S, Drummond C, Oyefeso A, Phillips T, Deluca P, Perryman K, et al. Low identification of alcohol use disorders in general practice in England. *Addict Abingdon Engl.* 2008 May;103(5):766–73.
142. Khadjesari Z, Marston L, Petersen I, Nazareth I, Walters K. Alcohol consumption screening of newly-registered patients in primary care: a cross-sectional analysis. *Br J Gen Pr.* 2013 Oct;63(615):e706–12.
143. Babor TE, Higgins-Biddle J, Dauser D, Higgins P, Burleson JA. Alcohol screening and brief intervention in primary care settings: implementation models and predictors. *J Stud Alcohol.* 2005 May 1;66(3):361–8.
144. Mäkelä P, Havio M, Seppä K. Alcohol-related discussions in health care—a population view. *Addiction.* 2011 Jul 1;106(7):1239–48.
145. Johansson K, Bendtsen P, Akerlind I. Early intervention for problem drinkers: readiness to participate among general practitioners and nurses in Swedish primary health care. *Alcohol Alcohol Oxf Oxf.* 2002 Feb;37(1).

146. Adams P, Powell A, McCormick R, Paton-Simpson G. Incentives for general practitioners to provide brief interventions for alcohol problems. *N Z Med J*. 1997 Aug;110(1049):291–4.
147. Aalto M, Pekuri P, Seppä K. Obstacles to carrying out brief intervention for heavy drinkers in primary health care: a focus group study. *Drug Alcohol Rev*. 2003 Jun;22(2):169–73.
148. Johnson M, Jackson R, Guillaume L, Meier P, Goyder E. Barriers and facilitators to implementing screening and brief intervention for alcohol misuse: a systematic review of qualitative evidence. *J Public Health*. 2011 Sep 1;33(3):412–21.
149. Aalto M, Pekuri P, Seppä K. Primary health care professionals' activity in intervening in patients' alcohol drinking: a patient perspective. *Drug Alcohol Depend*. 2002 Mar 1;66(1):39–43.
150. Beich A, Gannik D, Malterud K. Screening and brief intervention for excessive alcohol use: qualitative interview study of the experiences of general practitioners. *BMJ*. 2002 Oct 19;325(7369):870.
151. Lock CA, Kaner EF. Implementation of brief alcohol interventions by nurses in primary care: do non-clinical factors influence practice? *Fam Pract*. 2004 Jun 1;21(3):270–5.
152. Clinical Practice Research Datalink [Internet]. 2012. Available from: <http://www.cprd.com/intro.asp>
153. Walley T, Mantgani A. The UK General Practice Research Database. *lancet*. 350:1097–9.
154. Lockwood MJ. General Practice Research Database provides detailed anonymised data. *BMJ*. 1996 Sep 21;313(7059):757.
155. Kousoulis AA, Rafi I, de Lusignan S. The CPRD and the RCGP: building on research success by enhancing benefits for patients and practices. *Br J Gen Pract*. 2015 Jan 26;65(631):54–5.
156. Jick SS, Kaye JA, Vasilakis-Scaramozza C, Rodríguez LAG, Ruigómez A, Meier CR, et al. Validity of the General Practice Research Database. *Pharmacother J Hum Pharmacol Drug Ther*. 2003 May 1;23(5):686–9.
157. Chen Y-C, Wu J-C, Haschler I, Majeed A, Chen T-J, Wetter T. Academic Impact of a Public Electronic Health Database: Bibliometric Analysis of Studies Using the General Practice Research Database. *PLoS ONE*. 2011 Jun 22;6(6):e21404.
158. Clinical Practice Research Datalink: CPRD Bibliography [Internet]. 2015. Available from: <http://www.cprd.com/bibliography/>

159. Herrett E, Thomas S, Schoonen M, Smeeth L, and Hall A. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol*. 2010;69(1):4–14.
160. Benson T. The history of the Read Codes: the inaugural James Read Memorial Lecture 2011. *Inform Prim Care*. 2011;19(3):173–82.
161. Chisholm J. The Read clinical classification. *BMJ*. 1990 Apr 28;300(6732).
162. NHS Information Centre. Hospital Episodes Statistics [Internet]. Health & Social Care Information Centre. 2015. Available from: <http://www.hscic.gov.uk/hes>
163. Williams T, van Staa T, Puri S, Eaton S. Recent advances in the utility and use of the General Practice Research Database as an example of a UK Primary Care Data resource. *Ther Adv Drug Saf*. 2012 Apr 1;3(2):89–99.
164. Eaton S, Williams T, Puri S, van Staa T. The feasibility of linking the English Hospital Episode Statistics to the GPRD. *Pharmacoepidemiol Drug Saf*. 2008;17(S214).
165. Health and Social Care Information Centre(HSCIC). 2015. Available from: <http://www.hscic.gov.uk/>
166. Douglas I, Evans S, Rawlins MD, Smeeth L, Tabrizi SJ, Wexler NS. Juvenile Huntington's disease: a population-based study using the General Practice Research Database. *BMJ Open* [Internet]. 2013 Jan 1;3(4). Available from: <http://bmjopen.bmj.com/content/3/4/e002085.abstract>
167. Dommett RM, Redaniel T, Stevens MC, Martin RM, Hamilton W. Risk of childhood cancer with symptoms in primary care: a population-based case-control study. *Br J Gen Pract*. 2013 Jan 1;63(606):e22–9.
168. Office for National Statistics. 2011 Census - Population and Household Estimates for England and Wales, March 2011. Cardiff, UK: ONS; 2012.
169. Crooks CJ. Epidemiology of upper gastrointestinal bleeding. Ph.D. Thesis. University Of Nottingham: UK.; 2013.
170. Audit Commision. Improving data quality in the NHS: annual report on the PbR assurance programme. London.; 2010.
171. Office for National Statistics. General Lifestyle Survey Overview- a report on the 2011 General Lifestyle Survey: Drinking. 2013.
172. Ratib S, Fleming KM, Crooks CJ, Aithal GP, West J. 1 and 5 year survival estimates for people with cirrhosis of the liver in England, 1998-2009: a large population study. *J Hepatol*. 2014 Feb;60(2):282–9.

173. Lewis JD, Bilker WB, Weinstein RB, Strom BL. The relationship between time since registration and measured incidence rates in the General Practice Research Database. *Pharmacoepidemiol Drug Saf.* 2005 Jul 1;14(7):443–51.
174. Rothman K., Greenland S, Lash T. *Modern Epidemiology.* 3rd Edition. Philadelphia, PA: Lippincott, Williams & Wilkins.
175. Saunders JB, Davis M, Williams R. Do women develop alcoholic liver disease more readily than men? *Br Med J Clin Res Ed.* 1981 Apr 4;282(6270):1140–3.
176. Walker A, O'Brien M, Traynor J, et al. *Living in Britain: results from the 2001 General Household Survey.* London: HMSO, 2002;
177. Sattar G, Glen F, Diaper A. *General Household Survey Report 2004: Overview report.* London: Office for National Statistics 2005;
178. Office for National Statistics. *General Lifestyle Survey: a report on the 2009 General Lifestyle.* Office for National Statistics 2011;
179. Bertakis KD, Azari R, Helms LJ, Callahan EJ, Robbins JA. Gender differences in the utilization of health care services. *J Fam Pract.* 2000 Feb;49(2):147–52.
180. Hippisley-Cox J, Vinogradova Y. Trend in consultation rates in general practice 1995 to 2008: analysis of the QRESEARCH database. The NHS Information Centre, 2009;
181. Hunt K, Adamson J, Hewitt C, Nazareth I. Do women consult more than men? A review of gender and consultation for back pain and headache. *J Health Serv Res Policy.* 2011 Apr;16(2):108–17.
182. Hunt K, Ford G, Harkins L, Wyke S. Are Women More Ready to Consult than Men? Gender Differences in Family Practitioner Consultation for Common Chronic Conditions. *J Health Serv Res Policy.* 1999 Apr 1;4(2):96–100.
183. Wang Y, Hunt K, Nazareth I, Freemantle N, Petersen I. Do men consult less than women? An analysis of routinely collected UK general practice data. *BMJ Open* [Internet]. 2013 Aug 1;3(8). Available from: <http://bmjopen.bmj.com/content/3/8/e003320.abstract>
184. Heather N. Can screening and brief intervention lead to population-level reductions in alcohol-related harm? *Addict Sci Clin Pract.* 2012;7(15).
185. Roche AM, Toby Freeman. Brief interventions: good in theory but weak in practice. *Drug Alcohol Rev.* 2004 Mar 1;23(1):11–8.

186. Kaner EFS, Heather N, Mcavoy BR, Lock CA, Gilvarry E. Intervention for excessive alcohol consumption in primary health care: attitudes and practices of English General Practitioners. *Alcohol Alcohol*. 1999 Jul 1;34(4):559–66.
187. Nilsen P, Aalto M, Bendtsen P, Seppä K. Effectiveness of strategies to implement brief alcohol intervention in primary healthcare. *Scand J Prim Health Care*. 2006 Jan 1;24(1):5–15.
188. Grant BF. Prevalence and correlates of alcohol use and DSM-IV alcohol dependence in the United States: results of the National Longitudinal Alcohol Epidemiologic Survey. *J Stud Alcohol*. 1997 Sep;58(5):464–73.
189. Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *The Lancet*. Jun 27;373(9682):2223–33.
190. Hubbard RB, Baldwin DR. Diagnosing lung cancer earlier in the UK. *Thorax*. 2010 Sep 1;65(9):756–8.
191. Corner J, Hopkinson J, Fitzsimmons D, Barclay S, Muers M. Is late diagnosis of lung cancer inevitable? Interview study of patients' recollections of symptoms before diagnosis. *Thorax*. 2005 Apr 1;60(4):314–9.
192. Hamilton W. Cancer diagnosis in primary care. *Br J Gen Pract*. 2010 Feb 1;60(571):121–8.
193. Georghiou T, Steventon A, Billings J, Blunt I, Lewis G, Bardsley M. Predictive risk and health care: an overview. [Internet]. London: Nuffield Trust, 2011; Available from: <http://www.nuffieldtrust.org.uk/publications/predictive-risk-and-health-care-overview>
194. Dixon J, Bardsley M. Predictive risk modelling using routine data: underexploited potential to benefit patients. *J Health Serv Res Policy*. 2012 Jul 1;17(3):131–2.
195. NHS-Leeds North Clinical Commissioning Group. Risk Stratification (Pro-Active Care Management). NHS 2014.
196. Rehm J, Trevisan M. Alcohol-Related Morbidity and Mortality [Internet]. National Institute on Alcohol Abuse and Alcoholism; 2003. Available from: <http://pubs.niaaa.nih.gov/publications/arh27-1/39-51.htm>
197. Adams LA, Sanderson S, Lindor KD, Angulo P. The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies. *J Hepatol*. 2005 Jan;42(1):132–8.

198. Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. *Hepatol Baltim Md*. 1999 Dec;30(6):1356–62.
199. Hickman IJ, Macdonald GA. Impact of Diabetes on the Severity of Liver Disease. *Am J Med*. 2007 Oct;120(10):829–34.
200. Petrides AS. [Hepatogenic diabetes: pathophysiology, therapeutic options and prognosis]. *Z Für Gastroenterol*. 1999 Jun;Suppl 1:15–21.
201. Deschenes M, Somberg KA. Effect of transjugular intrahepatic portosystemic shunt (TIPS) on glycemic control in cirrhotic patients with diabetes mellitus. *Am J Gastroenterol*. 1998 Mar;93(3).
202. Picardi A, D’Avola D, Gentilucci UV, Galati G, Fiori E, Spataro S, et al. Diabetes in chronic liver disease: from old concepts to new evidence. *Diabetes Metab Res Rev*. 2006 Aug;22(4):274–83.
203. Sasco AJ, Secretan MB, Straif K. Tobacco smoking and cancer: a brief review of recent epidemiological evidence. *Trends Diagn Ther Lung Cancer*. 2004 Aug;45, Supplement 2(0):S3–9.
204. Gandini S, Botteri E, Iodice S, Boniol M, Lowenfels AB, Maisonneuve P, et al. Tobacco smoking and cancer: a meta-analysis. *Int J Cancer J Int Cancer*. 2008 Jan 1;122(1):155–64.
205. Dossus L, Boutron-Ruault M-C, Kaaks R, Gram IT, Vilier A, Fervers B, et al. Active and passive cigarette smoking and breast cancer risk: results from the EPIC cohort. *Int J Cancer J Int Cancer*. 2014 Apr 15;134(8):1871–88.
206. American Psychiatric Association(APA). *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,Text Revision*. Washington DC: APA,2000;
207. Shivani R, Goldsmith J, Anthenelli R. Alcoholism and Psychiatric disorders: Diagnosctic challenges. *National Institute on Alcohol Abuse and Alcoholism*; 2002.
208. Nilsen P. Brief alcohol intervention—where to from here? Challenges remain for research and practice. *Addiction*. 2010 Jun 1;105(6):954–9.
209. Nilsen P, Holmquist M. Alcohol Issues in Daily healthcare. The Risky Drinking Project: Background, Strategy and Results. *Swed Natl Inst Public Health Stockh*. 2010;
210. Heather N. WHO Collaborative Project on Identification and Management of Alcohol-Related Problems in Primary Health Care. Development of Country-wide Strategies for Implementing Early Identification and Brief Intervention in Primary Health Care. Report to the World Health

Organization on Phase IV. [Internet]. Geneva:World Health Organisation, Department of Mental Health and Substance Abuse; 2006 [cited 2015 Jun 10]. Available from:
http://www.who.int/substance_abuse/publications/identification_management_alcoholproblems_phaseiv.pdf

211. Afana A, Dalgard OS, Bjertness E, Grunfeld B. The ability of general practitioners to detect mental disorders among primary care patients in a stressful environment: Gaza Strip. *J Public Health Med.* 2002 Dec;24(4):326–31.
212. Maginn S, Boardman AP, Craig TKJ, Haddad M, Heath G, Stott J. The detection of psychological problems by General Practitioners--influence of ethnicity and other demographic variables. *Soc Psychiatry Psychiatr Epidemiol.* 2004 Jun;39(6):464–71.
213. Fleury M-J, Imboua A, Aubé D, Farand L, Lambert Y. General practitioners' management of mental disorders: A rewarding practice with considerable obstacles. *BMC Fam Pract.* 2012;13:19–19.
214. Wittchen H-U, Mühlig S, Beesdo K. Mental disorders in primary care. *Dialogues Clin Neurosci.* 2003 Jun;5(2):115–28.
215. Department of Health. 2010 to 2015 government policy: mental health service reform. Department of Health, UK; 2013.
216. Jones L, Bellis M, Dedman D, Sumnall H, Torque K Alcohol-attributable fractions for England: alcohol-attributable mortality and hospital admissions. Centre for Public health- Liverpool JohnMoore University. 2008.
217. Tellez-Zenteno JF, Patten SB, Jetté N, Williams J, Wiebe S. Psychiatric Comorbidity in Epilepsy: A Population-Based Analysis. *Epilepsia.* 2007 Dec 1;48(12):2336–44.
218. Gaitatzis A, Trimble MR, Sander JW. The psychiatric comorbidity of epilepsy. *Acta Neurol Scand.* 2004 Oct 1;110(4):207–20.
219. Mitchell AJ, Meader N, Bird V, Rizzo M. Clinical recognition and recording of alcohol disorders by clinicians in primary and secondary care: meta-analysis. *Br J Psychiatry J Ment Sci.* 2012 Aug;201:93–100.
220. Taggar J, Coleman T, Lewis S, Szatkowski L. The impact of the Quality and Outcomes Framework (QOF) on the recording of smoking targets in primary care medical records: cross-sectional analyses from The Health Improvement Network (THIN) database. *BMC Public Health.* 2012;12(1):329.

221. Hamilton FL, Lavery AA, Gluvajic D, Huckvale K, Car J, Majeed A, et al. Effect of financial incentives on delivery of alcohol screening and brief intervention (ASBI) in primary care: longitudinal study. *J Public Health* [Internet]. 2013 Dec 26; Available from: <http://jpubhealth.oxfordjournals.org/content/early/2013/12/26/pubmed.fdt121.abstract>
222. Carlisle D. Quality and outcomes framework. Points mean prizes for GPs, but what's in it for patients? *Health Serv J*. 2005;115:16–7.
223. Michie S, Hyder N, Walia A, West R. Development of a taxonomy of behaviour change techniques used in individual behavioural support for smoking cessation. *Addict Behav*. 2011 Apr;36(4):315–9.
224. Michie S, Whittington C, Hamoudi Z, Zarnani F, Tober G, West R. Identification of behaviour change techniques to reduce excessive alcohol consumption. *Addiction*. 2012 Aug 1;107(8):1431–40.
225. Chamberlain C, O'Mara-Eves A, Oliver S, Caird JR, Perlen SM, Eades SJ, et al. Psychosocial interventions for supporting women to stop smoking in pregnancy. *Cochrane Database Syst Rev*. 2013;10:CD001055.
226. Wallace P, Cutler S, Haines A. Randomised controlled trial of general practitioner intervention in patients with excessive alcohol consumption. *BMJ*. 1988 Sep 10;297(6649):663–8.
227. Prochaska JO, Velicer WF. The transtheoretical model of health behavior change. *Am J Health Promot AJHP*. 1997 Oct;12(1):38–48.
228. Hogan WR, Wagner MM. Free-text fields change the meaning of coded data. *Proc AMIA Annu Fall Symp*. 1996;517–21.

Appendices

Appendix 1: Brief description of alcohol attributable fractions and estimating of alcohol related harm

The Alcohol-attributable fraction (AAF) of any disease is defined as the proportion of a disease that is attributable to alcohol use. This fraction value is very important because it is the basis of estimating alcohol related burden. So for example, for conditions where the AAF is 1(100%) i.e. conditions where alcohol is reported to be responsible for all cases e.g. alcoholic liver disease, all cases of the disease in a given population will be included when estimating alcohol related burden within that population. However for partially attributable conditions e.g. falls and certain cancers only the fraction specified by the AAF value will be included.

Conditions where alcohol is responsible for all cases are referred to as “wholly alcohol attributable conditions” while the remaining conditions where alcohol is a contributory cause are referred to “partially alcohol attributable conditions”.

For diseases which are not wholly attributable to alcohol, AAFs are estimated by comparing the population risk of the disease under current conditions to a hypothetical scenario where no one has consumed alcohol. This is achieved by using information on the distribution of drinking patterns and the risks of disease in people drinking at different levels of alcohol consumption compared to abstainers. While there are several limitations to this method, not least the accuracy of the data on drinking patterns and the assumption of causality between alcohol and assessed diseases, this technique is widely used both in the UK and internationally and is considered the standard. AAF's in England for diseases partially attributable to alcohol are calculated by the North West Public Health Observatory. These AAFs are then applied annually to

hospital episode statistics and mortality data to estimate the total proportion of admissions cases and deaths caused by alcohol consumption each year.

Appendix 2: Code list used to identify supportive evidence for incident cases of alcoholic psychosis identified in only CPRD data.

ICD-10	Code description
F059	Delirium, unspecified
F067	Mild cognitive disorder
F09	Unspecified organic or symptomatic mental disorder
F100	Mental & behav dis due to use of alcohol: acute intoxication
F101	Mental and behav dis due to use of alcohol: harmful use
F102	Mental and behav dis due to use of alcohol: dependence synd
F103	Mental and behav dis due to use of alcohol: withdrawal state
F104	Men & behav dis due alcohol: withdrawal state with delirium
F106	Mental and behav dis due to use of alcohol: amnesic syndrome
F112	Mental & behav dis due to use of opioids; dependence syndrome
F125	Mental & behav dis due use cannabinoids; psychotic disorder
F132	Men & behav dis due use seds/hypnotics: dependence syndrome
F171	Men & behav dis due use tobacco: harmful use
F172	Men & behav dis due use tobacco: dependence syndrome
F190	Men & behav dis multiple/psychoact drug: acute intox
F192	Men & behav dis multiple/psychoact drug: dependence syndrome
F195	Men & behav dis multiple/psychoact drug: psychotic disorder
F200	Paranoid schizophrenia
F209	Schizophrenia, unspecified
F21	Schizotypal disorder
F220	Delusional disorder
F230	Acute polymorphic psychot disord without symp of schizoph'a
F233	Other acute predominantly delusional psychotic disorders
F239	Acute and transient psychotic disorder, unspecified
F259	Schizoaffective disorder, unspecified
F28	Other nonorganic psychotic disorders
F29	Unspecified nonorganic psychosis
F302	Mania with psychotic symptoms
F319	Bipolar affective disorder, unspecified
F321	Moderate depressive episode
F323	Severe depressive episode with psychotic symptoms
F329	Depressive episode, unspecified
F339	Recurrent depressive disorder, unspecified
F400	Agoraphobia
F402	Specific (isolated) phobias

F412	Mixed anxiety and depressive disorder
F419	Anxiety disorder, unspecified
F430	Acute stress reaction
F458	Other somatoform disorders
F601	Schizoid personality disorder
F819	Developmental disorder of scholastic skills, unspecified
F99	Mental disorder, not otherwise specified
X609	Occurrence at unspecified place
X610	Occurrence at home
X619	Occurrence at unspecified place
X640	Occurrence at home
X649	Occurrence at unspecified place
X650	Occurrence at home
X659	Occurrence at unspecified place
X780	Occurrence at home

Appendix 3: Code list used to identify supportive evidence for incident cases of alcoholic psychosis identified in HES data.

Medcode	Read code	Read term
29333	13L3.00	Relative - psychotic illness
5752	146..00	H/O: psychiatric disorder
24484	146Z.00	H/O: psychiatric disorder NOS
4874	2232	O/E - mentally confused
8194	225..11	O/E - mental state
4390	285..11	Psychotic condition, insight present
22644	286..11	Poor insight into psychotic condition
55797	6651	Psychiatric symptom changes
29931	6652	Mental state
4246	6664	Mental handicap problem
68132	6894	Mental retardation screen
6982	69F..00	Mental Health Act examination
22126	69FZ.00	Mental Health Act exam NOS
10835	6A6..00	Mental health review
30732	6A60.00	Mental health review follow-up
90108	7P22.00	Rehabilitation for psychiatric disorders
8419	8A2..00	Psychiatric monitoring
31278	8A21.00	Psychiatric observation
29777	8A2Z.00	Psychiatric monitoring NOS
12035	8BM0.00	Mental health medication review
32960	8CE9.00	Mental health information leaflet given
12469	8CM2.00	Psychiatry care plan
97639	8CM9.00	Mental health care programme approach contingency plan
18757	8CQ..00	Mental health crisis plan
51383	8CQ0.00	Completion of mental health crisis plan
97742	8CQ1.00	Mental health care programme approach crisis plan
98919	8CQ1.11	Mental health CPA crisis plan available
12470	8CR7.00	Mental health personal health plan
95965	8CY..00	Mental Health Care Programme Approach
101748	8Ce7.00	Preferred place of care - mental health unit
7503	8H23.00	Admit psychiatric emergency
3488	8H23000	Emerg psychiatric admisss MHA
95163	8H2T.00	Emergency voluntary psychiatric admission Mental Health Act
21638	8H34.00	Psychiatric day care
4711	8H38.00	Non-urgent psychiatric admisn.
2189	8H49.00	Psychiatric referral
18872	8H4P.00	Referral to child psychiatrist
24504	8H7A.00	Refer to mental health worker

24157	8HB8.00	Mental therapy follow-up
52032	8HBK.00	Mental health triage nurse follow up
12285	8HHR.00	Referral to child and adolescent psychiatry service
13703	8HHn.00	Referral to non NHS mental health community service
12365	8HHo.00	Referral to older age community mental health team
41071	8HHr.00	Referral for mental health self-help literature
12447	8HHu.00	Referral to primary care mental health gateway worker
41040	8HHv.00	Referral to primary care mental health graduate worker
27640	8HJ3.00	Psychiatric self-referral
24502	8HK9.00	Psychiatric D.V. requested
21384	8HL9.00	Psychiatry D.V. done
21625	8HM9.00	Listed for Psychiatric admissn
6282	8HT6.00	Referral to developmental clinic
13677	8HVO.00	Private referral to psychiatrist
12053	8Hc..00	Referral to mental health team
10236	8Hc0.00	Referral to community mental health team
11449	8Hc1.00	Referral to mental health crisis team
84212	8Hc2.00	Referral to primary care mental health team
32846	8Hg7.00	Discharged from care of mental health triage nurse
93427	8Hg9.00	Discharged from community mental health service
95967	8HgB.00	Discharged by mental health primary care worker
95936	8HIB.00	Urgent referral to psychiatrist
97570	8HID.00	Referral to forensic psychiatrist
102650	8IE5.00	Mental health assessment declined
34444	918d.00	Carer of a person with mental health problem
70680	9239	FP22-in mental hospital
7920	9H...00	Mental health administration
11265	9H6..00	On national service framework mental health register
12114	9H7..00	Removed from severe mental illness register
11166	9H8..00	On severe mental illness register
32589	9H9..00	Mental health annual physical examination done
16047	9HZ..00	Mental health admin. NOS
2764	9N1T.00	Seen in psychiatry clinic
25516	9N2a.00	Seen by community psychiatric nurse
46644	9N2q.00	Seen by primary care graduate mental health worker
46651	9N2r.00	Seen by mental health triage nurse
59872	9N2v.00	Seen by primary care mental health gateway worker
93440	9N2z.00	Seen by child and adolescent mental health service
10707	9N4N.00	Did not attend mental health appointment
30727	9N4g.00	DNA - Did not attend psychiatry clinic
43897	9N4j.00	DNA - Did not attend community psychiatric nurse review
30728	9N4t.00	DNA - Did not attend mental health review
102636	9N5F.00	Patient initiated encounter with mental health crisis team
93630	9N6h.00	Referral by mental health service

59131	9NI6.00	Psychiatric outreach clinic
90891	9NJb.00	In-house psychiatry first appointment
88736	9NJc.00	In-house psychiatry discharge
84412	9NJd.00	In-house psychiatry follow-up appointment
30574	9NN4.00	Has community mental health team key worker
18444	9NN5.00	Under care of psychiatrist
10308	9NN7.00	Under care of mental health team
19222	9NNM.00	Under care of community psychiatric nurse
47064	9NNQ.00	Under care of hospital psychiatric team
94698	9Nk6.00	Seen in mental health clinic
96940	9No0.00	Seen in child and adolescent psychiatry clinic
30463	9Ol..00	Mental health monitoring administration
34343	9OI0.00	Mental health monitoring first letter
34344	9OI1.00	Mental health monitoring second letter
34345	9OI2.00	Mental health monitoring third letter
45756	9OI3.00	Mental health monitoring verbal invitation
72385	9OI4.00	Mental health monitoring telephone invite
53715	9bA..00	Psychiatry
95599	9bA1.00	Mental illness (specialty)
39127	9bA2.00	Child and adolescent psychiatry
72941	9bA3.00	Forensic psychiatry
73346	9bA5.00	Old age psychiatry
34360	9h9..00	Exception reporting: mental health quality indicators
11774	9h91.00	Except from mental health quality indicators: Patient unsuit
11750	9h92.00	Except from mental health quality indicators: Informed diss
3630	E....00	Mental disorders
7233	E0...00	Organic psychotic conditions
33707	E00..00	Senile and presenile organic psychotic conditions
17770	E130.11	Psychotic reactive depression
3636	E13z.11	Psychotic episode NOS
42410	E2z..00	Neuroses or other mental disorder NOS
9971	Eu...00	[X]Mental and behavioural disorders
30034	Eu1..00	[X]Mental and behavioural disorders due to psychoactive subs
5611	Eu10.00	[X]Mental and behavioural disorders due to use of alcohol
44299	Eu10000	[X]Mental & behav dis due to use alcohol: acute intoxication
21879	Eu10100	[X]Mental and behav dis due to use of alcohol: harmful use
39327	Eu10200	[X]Mental and behav dis due to use alcohol: dependence syndr
20514	Eu10300	[X]Mental and behav dis due to use alcohol: withdrawal state
12353	Eu10500	[X]Mental & behav dis due to use alcohol: psychotic disorder
39799	Eu10600	[X]Mental and behav dis due to use alcohol: amnesic syndrome
41317	Eu13.00	[X]Mental and behavioural dis due use sedatives/hypnotics
64210	Eu13000	[X]Mental & behav dis due seds/hypntcs: acute intoxication
44330	Eu13200	[X]Mental and behav dis due to seds/hypntcs: dependence synd

62449	Eu21.14	[X]Prepsychotic schizophrenia
25019	Eu23.00	[X]Acute and transient psychotic disorders
11778	Eu23200	[X]Acute schizophrenia-like psychotic disorder
44503	Eu23y00	[X]Other acute and transient psychotic disorders
34168	Eu23z00	[X]Acute and transient psychotic disorder, unspecified
11973	Eu24.13	[X]Induced psychotic disorder
30985	Eu2y.00	[X]Other nonorganic psychotic disorders
13024	Eu30100	[X]Mania without psychotic symptoms
21065	Eu30200	[X]Mania with psychotic symptoms
37102	Eu30211	[X]Mania with mood-congruent psychotic symptoms
48632	Eu30212	[X]Mania with mood-incongruent psychotic symptoms
9667	Eu32200	[X]Severe depressive episode without psychotic symptoms
41989	Eu32211	[X]Single episode agitated depressn w/out psychotic symptoms
22806	Eu32212	[X]Single episode major depression w/out psychotic symptoms
59386	Eu32213	[X]Single episode vital depression w/out psychotic symptoms
12099	Eu32300	[X]Severe depressive episode with psychotic symptoms
24117	Eu32311	[X]Single episode of major depression and psychotic symptoms
24112	Eu32313	[X]Single episode of psychotic depression
98414	Eu32700	[X]Major depression, severe without psychotic symptoms
98417	Eu32800	[X]Major depression, severe with psychotic symptoms
11329	Eu33211	[X]Endogenous depression without psychotic symptoms
11252	Eu33212	[X]Major depression, recurrent without psychotic symptoms
29451	Eu33213	[X]Manic-depress psychosis,depressd,no psychotic symptoms
73991	Eu33214	[X]Vital depression, recurrent without psychotic symptoms
23731	Eu33311	[X]Endogenous depression with psychotic symptoms
28677	Eu33312	[X]Manic-depress psychosis,depressed type+psychotic symptoms
32941	Eu33313	[X]Recurr severe episodes/major depression+psychotic symptom
16861	Eu33315	[X]Recurrent severe episodes of psychotic depression
37531	Eu62100	[X]Enduring personality change after psychiatric illness
35200	Euz..00	[X]Mental disorder, not otherwise specified
22359	Euz..11	[X]Mental illness NOS
27703	Ey...00	Other specified mental disorders
10945	Ez...00	Mental disorders NOS
11092	ZL1B.00	Under care of psychiatrist
11954	ZL1B100	Under care of child and adolescent psychiatrist
32625	ZL1B200	Under care of forensic psychiatrist
48562	ZL1B300	Under care of liaison psychiatrist
32546	ZL1B411	Under care of elderly mentally ill psychiatrist
26342	ZL1B412	Under care of old age psychiatrist
32847	ZL1B600	Under care of rehabilitation psychiatrist
32684	ZL22E00	Under care of psychiatric nurse
25333	ZL23100	Under care of community psychiatric nurse
32602	ZL31400	Under care of mental health counsellor

10002	ZL5B.00	Referral to psychiatrist
11071	ZL5B100	Referral to child and adolescent psychiatrist
10026	ZL5B111	Referral to child psychiatrist
36728	ZL5B300	Referral to liaison psychiatrist
44910	ZL5B400	Referral to rehabilitation psychiatrist
9868	ZL62E00	Referral to psychiatric nurse
10828	ZL73400	Referral to mental health counsellor
9822	ZL9D.00	Seen by psychiatrist
10027	ZL9D100	Seen by child and adolescent psychiatrist
25555	ZL9D200	Seen by forensic psychiatrist
28714	ZL9D300	Seen by liaison psychiatrist
28725	ZL9D411	Seen by psychiatrist for the elderly mentally ill
28720	ZL9D412	Seen by old age psychiatrist
38954	ZL9D500	Seen by psychiatrist for mental handicap
28802	ZL9D600	Seen by rehabilitation psychiatrist
25134	ZLA2E00	Seen by psychiatric nurse
7950	ZLA3100	Seen by community psychiatric nurse
11425	ZLB5.00	Seen by mental health counsellor
11133	ZLD1400	Discharge by mental health counsellor
25459	ZLD2a00	Discharge by psychiatrist
25314	ZLD2b00	Discharge by child and adolescent psychiatrist
25554	ZLD2c00	Discharge by forensic psychiatrist
32537	ZLD2e12	Discharge by psychiatrist for the elderly mentally ill
45983	ZLD2g00	Discharge by rehabilitation psychiatrist
32534	ZLD7C00	Discharge by psychiatric nurse
25528	ZLD8100	Discharge by community psychiatric nurse
25510	ZLE9.00	Discharge from psychiatry service
25846	ZLE9100	Discharge from child and adolescent psychiatry service
94758	ZLE9200	Discharge from forensic psychiatry service
53189	ZLE9300	Discharge from liaison psychiatry service
32093	ZLF2200	Discharge from psychiatry day hospital
59238	ZLF2311	Discharge from old age psychiatry day hospital
9945	ZQ3E.00	Mental health assessment
35326	ZQ3F.00	Planned mental health assessment
25262	ZQ3G.00	Emergency mental health assessment
30191	ZV11.00	[V]Personal history of mental disorder
93419	ZV11y00	[V]Personal history of other specified mental disorder
73954	ZV11z00	[V]Personal history of unspecified mental disorder
41355	ZV17000	[V]Family history of psychiatric condition
30182	ZV1A.00	[V]Family history of mental and behavioural disorders
25128	ZV40.00	[V]Mental and behavioural problems
31638	ZV40.12	[V]Mental problems
63785	ZV40200	[V]Other mental problems
55678	ZV40y00	[V]Other specified mental or behavioural problem

45309	ZV40z00	[V]Unspecified mental or behavioural problem
27866	ZV4By00	[V]Other physical and mental strain related to work
40414	ZV67300	[V]Psychotherapy/other treatment-mental disorder follow-up
23920	ZV69.00	[V]Psychiatric patient admission details
52742	ZV69000	[V]Psychiatric patient - not previously admitted
94762	ZV69111	[V]Psychiatric patient - previous admission this district
53030	ZV69211	[V]Psychiatric patient - previously admitted other district
37595	ZV70100	[V]General psychiatric examination requested by authority
9748	ZV70200	[V]Other or unspecified general psychiatric examination

Appendix 4: Code list for medications considered as supporting evidence for incident cases of alcoholic psychosis

Drug code (multilex code)	Drug substance name
17138001	agomelatine
4948001	alprazolam
11612001	amisulpride
2776002	amitriptyline hydrochloride
1656001	amitriptyline hydrochloride/chlordiazepoxide
5296002	amitriptyline hydrochloride/perphenazine
4958002	amobarbital sodium
2747001	amobarbital sodium/secobarbital sodium
5994002	amoxapine
12546001	aripiprazole
4901002	ascorbic acid/pyridoxine hydrochloride/tryptophan
4019001	benperidol
523002	bromazepam
5176001	buspirone hydrochloride
5072001	butobarbital
5311001	butriptyline hydrochloride
2966001	carbamazepine
652001	chloral hydrate
1743009	chloral hydrate/potassium bromide
3190002	chlordiazepoxide hydrochloride
6412001	chlorpromazine
5238001	chlorpromazine hydrochloride
926001	chlorprothixene
8619001	citalopram hydrobromide
7825001	citalopram hydrochloride
3351001	clobazam
3359001	clomipramine hydrochloride
3365001	clonazepam
6422001	cloral betaine
6404001	clozapine
2967001	cyclobarbitol calcium
1853001	desipramine hydrochloride
2783001	diazepam
3595001	dichloralphenazone
967002	dipotassium clorazepate

3688002	dosulepin hydrochloride
3691002	doxepin hydrochloride
3696001	droperidol
13001001	duloxetine hydrochloride
8328001	escitalopram oxalate
17423001	eslicarbazepine acetate
829001	flunitrazepam
5552001	fluoxetine hydrochloride
3495002	flupentixol dihydrochloride
3498001	fluphenazine hydrochloride
2365001	fluphenazine hydrochloride/nortriptyline hydrochloride
210002	flurazepam hydrochloride
3506002	fluvoxamine maleate
3750002	haloperidol
2655001	haloperidol decanoate
2887001	imipramine hydrochloride
3891001	iprindole
551001	iproniazid phosphate
3894001	isocarboxazid
887001	isopropamide iodide/trifluoperazine hydrochloride
53002	ketazolam
1146001	levomepromazine hydrochloride
1146002	levomepromazine maleate
4000001	lofepramine
2361001	loprazolam mesilate
4007002	lormetazepam
5993002	loxapine
4071002	maprotiline hydrochloride
650002	medazepam
8139001	melatonin
653001	methypylone
4190001	mianserin hydrochloride
11282001	mirtazapine
6250001	moclobemide
8637001	nefazodone hydrochloride
2772001	nitrazepam
4303001	nortriptyline hydrochloride
10432003	olanzapine
4332001	oxazepam
8374002	oxcarbazepine
469001	oxypertine
15473001	paliperidone
6509001	paroxetine hydrochloride
637001	pericyazine

1412001	perphenazine
622001	phenelzine sulphate
4483001	pimozide
1744009	potassium bromide/valerian extract
156001	prazepam
4603001	prochlorperazine maleate
2659001	prochlorperazine mesilate
6522001	promazine hydrochloride
2494001	protriptyline hydrochloride
11262003	quetiapine fumarate
11161001	reboxetine mesilate
6655001	remoxipride hydrochloride monohydrate
362002	risperidone
850002	secobarbital sodium
10187001	sertindole
6826001	sertraline hydrochloride
13789001	sodium oxybate
5393001	sodium valproate
4773001	sulpiride
562001	thioridazine hydrochloride
4855001	tranlycypromine sulphate
4857002	trazodone hydrochloride
4878002	triazolam
1925001	triclofos sodium
7376003	trifluoperazine hydrochloride
719001	trifluoperazine hydrochloride/tranlycypromine sulphate
4883002	trifluoperidol
4892002	trimipramine maleate
4900001	tryptophan
2371001	valproate semisodium
6983002	valproic acid
1663001	venlafaxine hydrochloride
1040001	viloxazine hydrochloride
11725002	zaleplon
7295001	zolpidem tartrate
6361001	zopiclone
1809002	zotepine
6480001	zuclopenthixol acetate
1232001	zuclopenthixol decanoate
178002	zuclopenthixol dihydrochloride

8.6

Appendix 5: Code list for alcohol related outcomes

Read code	Description
1361.11	Non-drinker alcohol
1361.12	Non-drinker alcohol
1361	Teetotaller
136M.00	Current non drinker
1362	Trivial drinker - <1u/day
136O.00	Moderate drinker
136N.00	Light drinker
136L.00	Alcohol intake within recommended sensible limits
136C.00	Ex-moderate drinker - (3-6u/d)
1362.12	Drinks occasionally
U801.00	[X]Eviden of alcohl involv blood alcohl level 20-39mg/100ml
136A.00	Ex-trivial drinker (<1u/day)
136B.00	Ex-light drinker - (1-2u/day)
1364	Moderate drinker - 3-6u/day
1363	Light drinker - 1-2u/day
1362.11	Drinks rarely
U800.00	[X]Eviden of alcohl involv blood alcohl level <20 mg/100 ml
136K.00	Alcohol intake above recommended sensible limits
136S.00	Hazardous alcohol use
136R.00	Binge drinker
U803.00	[X]Eviden of alcohl involv blood alcohl level 60-79mg/100ml
136W.00	Alcohol misuse
U802.00	[X]Eviden of alcohl involv blood alcohl level 40-59mg/100ml
136E.00	Ex-very heavy drinker-(>9u/d)
ZRk6.11	SADQ - Severity of alcohol dependence questionnaire
ZR1E.00	Alcohol dependence scale
U804.00	[X]Eviden of alcohl involv blood alcohl level 80-99mg/100ml
ZR1E.11	ADS - Alcohol dependence scale
E250100	Nondependent alcohol abuse, continuous
E250z00	Nondependent alcohol abuse NOS
1365	Heavy drinker - 7-9u/day
E23..12	Alcohol problem drinking
136Q.00	Very heavy drinker
E231z00	Chronic alcoholism NOS
136D.00	Ex-heavy drinker - (7-9u/day)
136T.00	Harmful alcohol use

E250.00	Nondependent alcohol abuse
136P.00	Heavy drinker
ZRBJ.00	Drinking problem scale
1366	Very heavy drinker - >9u/day
4I91.11	Breath alcohol level
ZRK9.11	SADD - Short alcohol dependence data
ZV4KC00	[V] Alcohol use
8CE1.00	Alcohol leaflet given
136F.00	Spirit drinker
388u.00	Fast alcohol screening test
1367	Stopped drinking alcohol
136Z.00	Alcohol consumption NOS
ZRa1100	Brief Michigan alcoholism screening test
136G.00	Beer drinker
1368	Alcohol consumption unknown
ZRVK.00	Last six months of drinking questionnaire
9k19.00	Alcohol assesment declined - enhanced services admin
ZRK9.00	Short alcohol dependence data
ZG23100	Advice on alcohol consumption
8CAM.00	Patient advised about alcohol
ZR1F.11	AUDIT - Alcohol use disorders identification test
8HHe.00	Referral to community drug and alcohol team
6892	Alcohol consumption screen
9k13.00	Alcohol questionnaire completed
ZRa1.11	MAST - Michigan alcoholism screening test
9k15.00	Alcohol screen - AUDIT completed
9k19.11	Alcohol assessment declined
ZR1G.00	Alcohol use inventory
ZV79100	[V]Screening for alcoholism
38D3.00	Alcohol use disorders identification test
8HKJ.00	Referral to alcohol brief intervention service
Z4B1.00	Alcoholism counselling
9k1B.00	Extended intervention for excessive alcohol consumptn complt
ZV6D600	[V]Alcohol abuse counselling and surveillance
38D2.00	Single alcohol screening questionnaire
ZR1F.00	Alcohol use disorders identification test
136H.00	Drinks beer and spirits
8CAv.00	Advised to contact primary care alcohol worker
ZR3f.00	Comprehensive drinker profile
67H0.00	Lifestyle advice regarding alcohol
136I.00	Drinks wine
38D4.00	Alcohol use disorder identificatn test consumptn questionnre
68S..00	Alcohol consumption screen
9k18.00	Alcohol screen - AUDIT PC completed

ZRk6.00	Severity of alcohol dependence questionnaire
136X.00	Alcohol units consumed on heaviest drinking day
44X4.00	Blood methanol level
136V.00	Alcohol units per week
ZR3f.11	CDP - Comprehensive drinker profile
9k17.00	Alcohol screen - AUDIT C completed
8HkG.00	Referral to specialist alcohol treatment service
ZC22200	Advice to change alcoholic drink intake
6792	Health ed. - alcohol
136..00	Alcohol consumption
9k11.00	Alcohol consumption counselling
9k1A.00	Brief intervention for excessive alcohol consumptn completed
67A5.00	Pregnancy alcohol advice
8H7p.00	Referral to community alcohol team
ZRBJ.11	DPS - Drinking problem scale
8IA7.00	Alcohol consumption screening test declined
ZRaU.00	Munich alcoholism test
ZRa1111	BMAST - Brief Michigan alcoholism screening test
9k16.00	Alcohol screen - fast alcohol screening test completed
ZRa1.00	Michigan alcoholism screening test
ZRR..00	Inventory of drinking situations
ZC2H.00	Advice to change alcohol intake
TJH3.00	Adverse reaction to alcohol deterrents
SM0..00	Alcohol causing toxic effect
Eu10z00	[X]Ment & behav dis due use alcohol: unsp ment & behav dis
Eu10513	[X]Alcoholic paranoia
Eu10100	[X]Mental and behav dis due to use of alcohol: harmful use
Eu10611	[X]Korsakov's psychosis, alcohol induced
2577.11	O/E - alcoholic breath
E231.00	Chronic alcoholism
E231300	Chronic alcoholism in remission
2577	O/E - breath - alcohol smell
SM01.00	Methyl alcohol causing toxic effect
9k1..00	Alcohol misuse - enhanced services administration
U1A9000	[X]Accident poison/exposure to alcohol at home
Eu10300	[X]Mental and behav dis due to use alcohol: withdrawal state
U209y00	[X]Int self poison alcohol other spec place
U60H311	[X] Adverse reaction to alcohol deterrents
E011z00	Alcohol amnestic syndrome NOS
E230.00	Acute alcoholic intoxication in alcoholism
E010.11	DTs - delirium tremens
ZV57A00	[V]Alcohol rehabilitation
T900.00	Accidental poisoning by alcoholic beverages
Eu10200	[X]Mental and behav dis due to use alcohol: dependence syndr

Z191400	Self-monitoring of alcohol intake
E01..00	Alcoholic psychoses
E230100	Continuous acute alcoholic intoxication in alcoholism
E230300	Acute alcoholic intoxication in remission, in alcoholism
ZV11311	[V]Problems related to lifestyle alcohol use
136J.00	Social drinker
E012.00	Other alcoholic dementia
U1A9.00	[X]Accident poisoning/exposure to alcohol
T901z00	Accidental poisoning by ethyl alcohol NOS
Eu10512	[X]Alcoholic jealousy
SLH3.00	Alcohol deterrent poisoning
U409.00	[X]Poisoning/exposure, ? intent, to alcohol
U1A9400	[X]Accid poison/expos alcohol in street/highway
U409400	[X]Pois/expos ?intent alcohol in street/highway
E011000	Korsakov's alcoholic psychosis
Eu10211	[X]Alcohol addiction
T901100	Accidental poisoning by methylated spirit
J617000	Chronic alcoholic hepatitis
8IAJ.00	Declined referral to specialist alcohol treatment service
E011200	Wernicke-Korsakov syndrome
8H35.00	Admitted to alcohol detoxification centre
E23..11	Alcoholism
Eu10000	[X]Mental & behav dis due to use alcohol: acute intoxication
E231000	Unspecified chronic alcoholism
E011100	Korsakov's alcoholic psychosis with peripheral neuritis
66e0.00	Alcohol abuse monitoring
E230200	Episodic acute alcoholic intoxication in alcoholism
9k10.00	Community detoxification registered
T90z.00	Accidental poisoning by alcohol NOS
9NN2.00	Under care of community alcohol team
U81..00	[X]Evid of alcohol involv determind by level of intoxication
U209000	[X]Int self poison/exposure to alcohol at home
Eu10712	[X]Chronic alcoholic brain syndrome
9k12.00	Alcohol misuse - enhanced service completed
U209z00	[X]Intent self poison alcohol unspecif place
E231100	Continuous chronic alcoholism
E014.11	Drunkenness - pathological
E250000	Nondependent alcohol abuse, unspecified
Eu10011	[X]Acute alcoholic drunkenness
E23..00	Alcohol dependence syndrome
SM01000	Methanol causing toxic effect
C150500	Alcohol-induced pseudo-Cushing's syndrome
66e..00	Alcohol disorder monitoring
E23z.00	Alcohol dependence syndrome NOS

J613.00	Alcoholic liver damage unspecified
E230.11	Alcohol dependence with acute alcoholic intoxication
E250300	Nondependent alcohol abuse in remission
Eu10514	[X]Alcoholic psychosis NOS
1462	H/O: alcoholism
8G32.00	Aversion therapy - alcoholism
SyuG000	[X]Toxic effect of other alcohols
E250.12	Hangover (alcohol)
E011.00	Alcohol amnestic syndrome
J613000	Alcoholic hepatic failure
U80..00	[X]Evidence of alcohol involv determin by blood alcohol level
7P22100	Delivery of rehabilitation for alcohol addiction
T90y.00	Accidental poisoning by other alcohols
E230z00	Acute alcoholic intoxication in alcoholism NOS
E015.00	Alcoholic paranoia
13ZY.00	Disqualified from driving due to excess alcohol
13Y8.00	Alcoholics anonymous
F375.00	Alcoholic polyneuropathy
J611.00	Acute alcoholic hepatitis
Z191100	Alcohol withdrawal regime
E250.13	Inebriety NOS
U1A9500	[X]Accid poison/expos alcohol trade/service area
E250.11	Drunkenness NOS
T90..00	Accidental poisoning by alcohol, NEC
J671000	Alcohol-induced chronic pancreatitis
Z191200	Planned reduction of alcohol consumption
F394100	Alcoholic myopathy
T901.00	Accidental poisoning by other ethyl alcohol and its products
F144000	Cerebellar ataxia due to alcoholism
9k14.00	Alcohol counselling by other agencies
U409z00	[X]Pois/expos ?intent to alcohol unspecif place
8BA8.00	Alcohol detoxification
J617.00	Alcoholic hepatitis
Z191211	Alcohol reduction programme
E250200	Nondependent alcohol abuse, episodic
E012000	Chronic alcoholic brain syndrome
E01yz00	Other alcoholic psychosis NOS
F11x011	Alcoholic encephalopathy
E014.00	Pathological alcohol intoxication
Eu10411	[X]Delirium tremens, alcohol induced
E013.00	Alcohol withdrawal hallucinosis
1D19.00	Pain in lymph nodes after alcohol consumption
ZV11300	[V]Personal history of alcoholism
E010.00	Alcohol withdrawal delirium

E250.14	Intoxication - alcohol
J610.00	Alcoholic fatty liver
E01y000	Alcohol withdrawal syndrome
U409000	[X]Poison/exposure ?intent, to alcohol at home
T902000	Accidental poisoning by methanol
E230000	Acute alcoholic intoxication, unspecified, in alcoholism
1B1c.00	Alcohol induced hallucinations
J153.00	Alcoholic gastritis
E010.12	Delirium tremens
8IAF.00	Brief intervention for excessive alcohol consumptn declined
Eu10212	[X]Chronic alcoholism
G555.00	Alcoholic cardiomyopathy
U1A9z00	[X]Accid poison/expos to alcohol unspecif place
E01y.00	Other alcoholic psychosis
E012.11	Alcoholic dementia NOS
Eu10400	[X]Men & behav dis due alcoh!: withdrawl state with delirium
R103.00	[D]Alcohol blood level excessive
Eu10800	[X]Alcohol withdrawal-induced seizure
U409200	[X]Pois/exp ?intent alcohol school/pub admin area
T902.00	Accidental poisoning by methyl alcohol
E231200	Episodic chronic alcoholism
Eu10213	[X]Dipsomania
E231.11	Dipsomania
U60H300	[X]Alcohol deterrents caus adverse effects in therapeut use
U209.00	[X]Intent self poison/exposure to alcohol
Eu10600	[X]Mental and behav dis due to use alcohol: amnesic syndrome
L255300	Maternal care for (suspected) damage to fetus from alcohol
F11x000	Cerebral degeneration due to alcoholism
Eu10.00	[X]Mental and behavioural disorders due to use of alcohol
E01z.00	Alcoholic psychosis NOS
Eu10711	[X]Alcoholic dementia NOS
Eu10500	[X]Mental & behav dis due to use alcohol: psychotic disorder
Z191.00	Alcohol detoxification
Eu10511	[X]Alcoholic hallucinosis
SM0y.00	Other alcohol causing toxic effect
T903300	Accidental poisoning by secondary propyl alcohol
F25B.00	Alcohol-induced epilepsy
Z19..00	Detoxification

Appendix 6: Code list for smoking

Read code	Description
137..11	Smoker - amount smoked
1371	Never smoked tobacco
1371.11	Non-smoker
1372	Trivial smoker - < 1 cig/day
1372.11	Occasional smoker
1373	Light smoker - 1-9 cigs/day
1374	Moderate smoker - 10-19 cigs/d
1375	Heavy smoker - 20-39 cigs/day
1376	Very heavy smoker - 40+cigs/d
1377	Ex-trivial smoker (<1/day)
1378	Ex-light smoker (1-9/day)
1379	Ex-moderate smoker (10-19/day)
137A.00	Ex-heavy smoker (20-39/day)
137B.00	Ex-very heavy smoker (40+/day)
137C.00	Keeps trying to stop smoking
137F.00	Ex-smoker - amount unknown
137G.00	Trying to give up smoking
137H.00	Pipe smoker
137J.00	Cigar smoker
137K.00	Stopped smoking
137L.00	Current non-smoker
137M.00	Rolls own cigarettes
137N.00	Ex pipe smoker
137O.00	Ex cigar smoker
137P.00	Cigarette smoker
137P.11	Smoker
137Q.00	Smoking started
137Q.11	Smoking restarted
137R.00	Current smoker
137S.00	Ex smoker
137T.00	Date ceased smoking
137V.00	Smoking reduced
137X.00	Cigarette consumption
137b.00	Ready to stop smoking
137c.00	Thinking about stopping smoking
137d.00	Not interested in stopping smoking
137e.00	Smoking restarted
137f.00	Reason for restarting smoking

137g.00	Cigarette pack-years
13p0.00	Negotiated date for cessation of smoking
6791	Health ed. - smoking
67H1.00	Lifestyle advice regarding smoking
8CAL.00	Smoking cessation advice
8H7i.00	Referral to smoking cessation advisor
8HTK.00	Referral to stop-smoking clinic
9N2k.00	Seen by smoking cessation advisor
9OO2.00	Refuses stop smoking monitor