Development of an alcohol intervention model for predicting healthcare costs, life years, quality-adjusted life years and using for economic evaluation

Pattara Leelahavarong

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Abstract

Objectives To develop an alcohol intervention model that predicts life years (LYs), quality adjusted life years (QALYs), and healthcare costs classified by the Alcohol Use Disorder Identification Test (AUDIT) screening tool and other various risk factors related to alcohol consumption. Furthermore, the developed model was transferred to the Thai setting.

Methods Eight Scottish Health Surveys from 1995-2012 were linked to Scottish morbidity records and death records for the period 1981 to the end of 2013. Parametric survival analysis was used to estimate the hazard risks of first alcohol-related and non-alcohol related hospitalisations and deaths. For men and women, multivariate data analyses were applied separately for each gender in modelling the utility score, risks of subsequent hospitalisation and annual healthcare costs within the follow-up period. Risk profiles were used for the covariates of the models as follows: age, socio-economic status, health condition, alcohol drinking (i.e. AUDIT and binge drinking), smoking, body mass index, and physical activity. According to the under-reporting bias of alcohol consumption among the survey population, this study adjusted the reported alcohol consumption using alcohol sales data. Multiple imputation approach was applied to deal with missing data. A health-state transition model with annual cycle length was developed to predict LYs, QALYs, lifetime costs, and cost-effectiveness. Probabilistic sensitivity analysis was also performed to deal with parameter uncertainty. Moreover, a methodological transferability protocol of the Thai study was detailed.

Results The sample size of the cohort was 46,230. The developed model showed the association between drinking and alcohol-related and non-alcohol related hospitalisations and deaths which were calculated as LYs and QALYs. Other risk factors were also taken into account that would likely affect the outcomes of interest. The modelling showed that an increasing AUDIT score and the number of cigarettes per day were associated with an increased risk of first alcohol-

attributable hospitalisation. Predicted outcomes for a male aged 30 year with high-risk drinking levels (AUDIT >7) were worse than males with low risk drinking (AUDIT ≤7), with approximately 5 LY gained and 7 QALY gained. The same results for females were obtained for high-risk drinking (AUDIT >4) compared to low-risk drinking (AUDIT ≤4), with approximately 10 LY gained and 12 QALY gained. Furthermore, an economic evaluation was performed to compare the no-intervention situation with a hypothetical health promotion intervention - which aimed to stop drinking (measured by the AUDIT) and smoking (measured by the number of cigarettes per day) behaviours. To compare the costs and benefits of the hypothetical intervention and no intervention over the lifetime period, a within-trial analysis combined with the developed model was able to capture both short- and longer-term consequences (i.e. LYs, QALYs, and healthcare costs) of the intervention. Finally, the model was able to compare cost-effectiveness ratio between risk behaviours without the new intervention and the modified risk behaviours when the new intervention is implemented.

Conclusions The study highlights the potential and importance of developing health economic models utilising data from routine national health surveys linked to national hospitalisation and death records. The developed framework can be used for further economic evaluation of alcohol interventions and other health behaviour change interventions. The framework can further be transferred to other country settings.

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Presentations and working papers

The following presentations and working papers were developed as part of this thesis:

Conference presentation, "Development and validation of alcohol-use disorder prediction model for monitoring and evaluation of alcohol consumption control programmes: Methodological challenges", Institute of Health & Wellbeing conference, 5th June 2014, University of Glasgow, UK

Conference presentation and paper, "Methodological challenges for development and validation of alcohol-use disorder prediction model for monitoring and evaluation of alcohol consumption control programmes", Health Economic Study Group conference 2014, 23rd - 25th June 2014, Glasgow Caledonian University, Glasgow, UK

Conference presentation and paper, "A policy model of alcohol-related harms for predicting life years and quality-adjusted life years" Health Economic Study Group conference 2015, 22nd -24th June 2015, Lancaster University, UK

Conference presentation and the Best Presentation awarded, "A policy model of alcohol-related harms for predicting life years and quality-adjusted life years", 4th HTAsiaLink conference 2015, 12th-15th May 2015, Chang Yung-Fa Charity Foundation (CYFCF), Taipei, Taiwan

Conference presentation, "Policy model of alcohol-related harms for predicting life years, quality-adjusted life years and lifetime healthcare costs", Farr Institute International Conference 2015: Data Intensive Health Care Research, 26th - 28th August 2015, St. Andrews, UK

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This thesis is dedicated to my parents and family.

Author's declaration

I declare that, except where explicit reference is made to the contribution of others, this thesis is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

Signature

Printed name

Pattara Leelahavarong, 2018

Abbreviations

AAF	Alcohol-attributable fraction
A&E	Accident and emergency
AUD	Alcohol-use disorder
AUDIT	Alcohol Use Disorder Identification Test
BMI	Body mass index
BOD	Burden of Disease
CBA	Cost-benefit analysis
CCA	Cost-consequence analysis
CEA	Cost-effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CI	Confidence interval
CIDI	Composite International Diagnostic Interview
CMA	Cost-minimization analysis
CUA	Cost-utility analysis
CVD	Cardiovascular disease
DALY	Disability-adjusted life years
eDRIS	electronic Data Research and Innovation Service
EM	Emergency
EQ-5D	EuroQol 5D
GDP	Gross domestic product
GLM	Generalised linear model
HRQoL	Health related quality of life
HTA	Health technology assessment
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
ISD	Information Services Division Scotland
LMIC	Low and middle-income countries
MALT	Munich Alcoholism Test
MAST	Michigan Alcoholism Screening Test

MCDM	Multi-criteria decision-making
NHS	National Health Service
NICE	National Institute of Health and Clinical Excellence
NMB	Net monetary benefit
NRS	National Record Scotland
NSS	National Services Scotland
NSSEC	National Statistics Socio-economic Classification[1]
OLS	Ordinary least squares
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life years
RCT	Randomized control trial
RMSE	Root mean square error
ROC	Receiver operator characteristic curve
SADQ	Severity of Alcohol Dependence Questionnaire
SAPM	Sheffield Alcohol Policy Model
SBI	Screening and brief intervention
SD	Standard deviation
SES	Socioeconomic status
SF-12	Short Form 12
SF-6D	Short Form 6D
SHeS	Scottish Health Surveys
SIMD	Scottish Index of Multiple Deprivation[2]
SMR	Scottish Morbidity Record
WHO	World Health Organisation
YLD	Years of life lived with disability
YLL	Years of life lost

[1] The National Statistics Socio-economic Classification (NSSEC) is a social classification system that attempts to classify groups on the basis of employment relations, based on characteristics such as career prospects, autonomy, mode of payment, and period of notice. There are five category systems in which participants are classified as managerial and professional, intermediate, small employers and own account workers, lower supervisory and technical, and semi-routine and routine occupations.

[2] The Scottish Index of Multiple Deprivation is the Scottish Government's official tool for identifying areas in Scotland concentrations of deprivation by incorporating several different aspects of deprivation (multiple-deprivations) and combining them into a single index. It is based on 38 indicators (published on 31 August 2016) across 7 individual domains of current income, employment, housing, health education, skills and training, telecommunications and geographic access to key services (travel times for driving and public transport).

Structure of thesis

The thesis consists of ten chapters, and each chapter starts with an introduction section of an overview and outline to orientate the reader as following.

Chapter 1 establishes the background information about alcohol drinking problems and burden of alcohol-related harms. Then, an overview evidence of alcohol policies in global and country levels, and the economic evaluation guidelines of public health and health promotion programme and applicable transferability of economic evaluation to other settings are presented. Due to increasing interest of alcohol policy evaluation, the importance of filling a knowledge gap in this area are described as well as a synopsis of the research methods and the implication of research findings.

Chapter 2 reviews the published literature of existing models for economic evaluation of alcohol intervention. Then, the rationale of developing a new alcohol intervention model is addressed.

Chapter 3 then describes the conceptual framework and objectives of the study. An analytical framework including input data sources, analytical methods, and expected output is addressed to outline the key methods used in this study. A health state transition model for estimating LYs, QALYs and lifetime healthcare cost is illustrated. The key data sources are identified and explained. Although this study has not required ethical approval due to the analysis using anonymised data with no identifiers, the ethical approval process for primary data collection is raised in this chapter.

Chapter 4 starts the first stage of analysis based on the analytical framework in Chapter 3 which is predicting the Alcohol Use Disorder Identification Test (AUDIT) score using SHeS to complete the AUDIT score where it is missing in SHeS waves 1995-2011. This chapter demonstrates a comparison of alternative

models for predicting AUDIT scores, and identifies the best predictive performance model to be used for the remaining analyses.

Chapter 5 presents the analysis of associations between alcohol-related hospitalisation and health-related quality of life in terms of utility decrement. The results will be used for estimating QALYs in the health state transition model.

Chapter 6 demonstrates the statistical analysis of SHeS-SMR linkage data to develop hazard function models of first event after survey date and death following the first hospitalisations using selected modifiable risk factors of study population. This chapter also describes the model validation and predicted life expectancy from the alcohol intervention model which is also re-calibrated by the latest Scottish life tables. The results are presented in term of predicted LYs for different risk profiles.

Chapter 7 describes how the developed health state transition model generates lifetime QALYs and healthcare costs. Modelling secondary events after first hospitalisation until death are carried out; moreover, modelling hospitalisation costs of all episodes following first admission is conducted. The key input parameters derived from previous analyses (described in Chapter 5) can be used for the health state transition model to generate lifetime QALYs and healthcare costs, and the results are also presented as subgroup by selected risk profiles.

Chapter 8 demonstrates how the alcohol intervention model could be used for economic evaluation of interventions which aim to change the selected risk factors, and the demonstration presents the impact of an intervention on changing LYs, QALYs and lifetime health service costs.

Chapter 9 discusses a developed protocol of further study in Thailand and methodological problem surrounding transferability to Thai context e.g. what Thai context specific data is required, working with limited data sources and

Thai's policy maker and public interest. The Thai study will evaluate the alcohol intervention and intervention implemented in Thailand.

Chapter 10 is a discussion and conclusion chapter to summarise the aims, approach and applications of developed alcohol intervention model not only for Scottish context but also opportunity of transfer to the Thai context.

Chapter 1: Introduction

1.1 Factors associated with alcohol consumption and alcohol-related harm

Alcohol-related harm is determined by the volume of alcohol consumed, the pattern of drinking, and the quality of alcohol consumed (Rehm et al., 2010a). In the context of the global burden of alcohol consumption, which is primarily concerned with alcohol's role in disease and injury, these three harms play different roles (WHO, 2014). For example, the toxic effect of alcohol is considered to cause many chronic conditions. For these conditions, alcohol shows a dose-response relationship, where the risk of onset of or death from the disease or condition depends on the total volume of alcohol consumed (Rehm et al., 2010a). This figure was also shown in a large cohort study in eight European countries, namely the European Prospective Investigation into Cancer and Nutrition (EPIC) study which found that alcohol consumption, especially drinking level higher than the upper recommended units, can result in higher incidences of cancer in both men (18.5%) and women (4%) (Schutze et al., 2011). In global burden estimates (WHO, 2014), dependence primarily appears as a mental disorder rather than as a risk factor for other health harms. The effect of dependence on other health harms is accounted for through the high volume and excessive patterns of consumption, for which dependence presumably contributes a large extent.

Furthermore, the pattern of drinking over time increases the risks of harm, particularly in heavy episodic drinking, which is defined as the consumption of 60 or more grams of pure alcohol (or >= 5 drinks per occasion in most countries) on at least one single occasion at least once a month (Roerecke and Rehm, 2010). The pattern of drinking is an important factor for many acute consequences of drinking such as alcohol poisoning, injury and violence, and intoxication (Rehm et al.,

2010a, Shield et al., 2013). Lastly, the quality of alcoholic beverages may also impact health and mortality, e.g. when home-made or illegally produced alcoholic beverages are contaminated with methanol or other very toxic substances (Rehm et al., 2010b). Unrecorded products are often available outside the regulated market (resulting, for example, in cheaper prices, different controls or no controls on availability), may increase overall consumption, and have also been linked to more heavy drinking episodes (Rehm et al., 2010b).

Figure 1-1 illustrates the conceptual causal model of alcohol consumption, intermediate mechanisms, and long-term consequences, as well as the influence of societal and demographic factors of alcohol consumption and alcohol-related harms (Shield et al., 2013, Rehm et al., 2010a). A variety of factors have been identified at societal- and individual-levels which affect the volume and patterns of consumption and can increase the risk of alcohol use disorders and other alcohol-related problems in individual drinkers and others such as family members (Babor et al., 2010a, Shield et al., 2013, Rehm et al., 2010a).

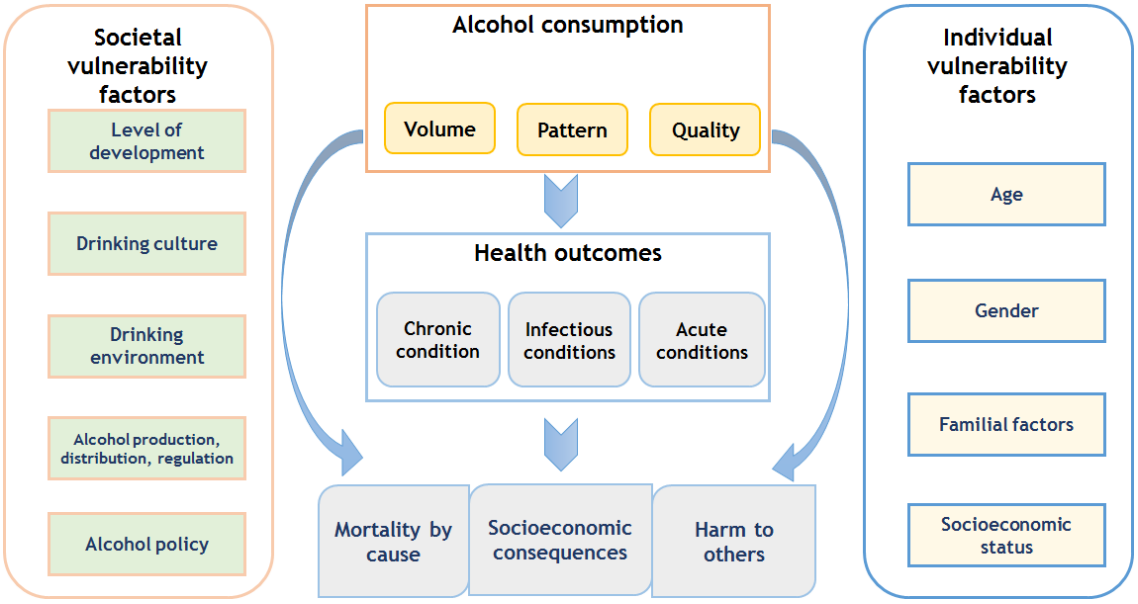


Figure 1-1 Conceptual causal model of alcohol consumption related to harms and vulnerability factors, i.e. societal and individual factors.

Adapted from (Rehm et al., 2010a, Shield et al., 2013)

1.1.1 Societal vulnerability factors

The societal factors include the following. First, economic development is the most important of the societal vulnerability factors related to alcohol consumption, as well as to alcohol-attributable disease burden (WHO, 2014, OECD, 2015). Emerging economies have seen a major relative increase in alcohol consumption (OECD, 2015). However, a recent published study concluded that the effects of declining macroeconomic conditions (represented by the increased unemployment rate) also increased problems related to alcohol consumption such as binge drinking, alcohol abuse, alcohol dependence and drink-driving (Davalos et al., 2012). These problems resulted in high mortality, burden of disease, and injury in the societies (WHO, 2014).

The second societal factor which affects alcohol consumption is the drinking environment such as private residences, licensed premises and other

settings such as parks and beaches. These environments may contribute to high levels of alcohol consumption resulting in higher risk of alcohol-related harms (WHO, 2014). For instance, alcohol consumption in commercial drinking environment, e.g. bars, pubs, and clubs - which are licensed for retail sales - may lead to high-risk drinking (Babor et al., 2010a). Thus, many establishments make these drinking locations prime targets for alcohol policies aimed at the prevention of alcohol-related problems.

The third factor is the level and effectiveness of alcohol control for production and distribution of alcohol, and alcohol regulations (Babor et al., 2010b). The scope and nature of alcohol-attributable disease burden and alcohol-related social harms provide a solid rationale for tackling harmful use of alcohol through national and international alcohol policies and interventions. The systematic review findings indicated that population-based policy options, which use taxation to regulate the demand for alcoholic beverages as well as restricting their availability and implementing bans on alcohol advertising, show effective and cost-effective results in reducing alcohol use disorders, alcohol attributable deaths, and disabilities at the population level (Anderson et al., 2009a, Anderson et al., 2009b, Chisholm et al., 2004).

1.1.2 Individual vulnerability factors

Many individual factors can influence alcohol consumption and alcohol-related harms (WHO, 2014). **T**he first factor is the difference in age (Bonnie and O'Connell, 2004, Healey et al., 2014, Richter et al., 2015, Hingson, 2010, Donovan, 2013, Delker et al., 2016). Young people were associated with a greater proportion of total alcohol consumed (Marshall, 2014), and underage drinking (less than aged 18 years) increased risks for alcohol dependence and abuse at later ages, alcohol-related motor vehicle crashes, and other unintentional injuries (Healey et al., 2014, Bonnie and O'Connell, 2004, Richter et al., 2015, Hingson, 2010, Miller et

al., 2006). However, alcohol-related harm among elderly people is due to somewhat different factors than alcohol-related harm among young people (WHO, 2014). While alcohol consumption generally declines with age, older drinkers typically consume alcohol more frequently than other age groups. Also, as people grow older, their bodies are typically less able to handle the same levels and patterns of alcohol consumption as in previous life years, leading to a high burden from unintentional injuries such as alcohol-related falls.

The second individual factor is the difference in gender. Alcohol consumption and its related harms among men have been greater than women (WHO, 2014, Delker et al., 2016, Probst et al., 2015b). Factors contributing to this include the fact that men are less often abstainers, and drink more frequently and in larger quantities. Harmful use of alcohol is the leading risk factor for death in males aged 15–59 years (Whiteford et al., 2013), yet there is evidence that women may be more vulnerable to alcohol-related harm from a given level of alcohol use or a particular drinking pattern (Wilsnack et al., 2013). The vulnerability of females to alcohol-related harm is a major public health concern because alcohol use among women has been increasing steadily in line with economic development and changing gender roles (Richman et al., 1995), and because it can have severe health and social consequences for newborns (McBride, 2014, Wilsnack et al., 2013).

The third individual factor is family history of alcohol use disorders. This is considered as a major vulnerability factor for both genetic and environmental reasons (Reboussin et al., 2012, Bellis et al., 2007, Guerrini et al., 2014). Multiple genes influence alcohol use initiation, metabolism, and reinforcing properties in different ways, contributing to increased susceptibility to the toxic, psychoactive, and dependence-producing properties of alcohol. Parents with alcohol use disorders display particular patterns of alcohol consumption and thereby increase the likelihood that their children will develop drinking patterns associated with

high risks when they are introduced to alcohol (Reboussin et al., 2012, Bellis et al., 2007). In addition, heavy drinking by parents affects family functioning, the parent–child relationship, and parenting practices, which in turn affects child development adversely.

The fourth is socioeconomic status (SES) related to alcohol drinking and its consequences. A range of national and international survey studies found that people in higher SES groups were more often drinkers and drank smaller amounts more frequently, whereas those in lower SES groups had a higher proportion of abstainers; however, those who drank did so more often in problematic ways (Grittner et al., 2013, Grittner et al., 2012, Bloomfield et al., 2006). Moreover, the recent systematic reviews examined the association between socioeconomic factors, mortality, and morbidity for a range of alcohol-attributable conditions (Jones et al., 2015b, Probst et al., 2014, Probst et al., 2015b). The reviews identified that people with lower SES appear to be more vulnerable to alcohol-related problems. These figures showed that lower SES is associated with higher mortality for alcohol-attributable causes – despite lower socioeconomic groups often reporting lower average levels of alcohol consumption defined as the Alcohol Harm Paradox (Smith and Foster, 2014). The potential vulnerabilities among lower SES groups are possibly due to the following: heavy drinking occasions more often, under-reporting of consumption, multiple 'unhealthy' behaviours, barriers to accessing health and alcohol related services, and the effects of poverty on health inequalities (Probst et al., 2014, Probst et al., 2015b, Smith and Foster, 2014).

1.1.3 Multiple alcohol-related behaviours

A growing evidence base suggests that risk behaviours often cluster or co-occur within individuals such as smoking, alcohol use, unhealthy diet, and lack of physical activity (McAloney et al., 2013, Schuit et al., 2002). Co-occurrence refers to concurrent (but independent) engagement in two or more risk behaviours;

clustering refers to underlying associations between co-occurring risk behaviours (Noble et al., 2015, McAloney et al., 2013). Systematic reviews of cross-sectional and longitudinal studies that investigated the most common combinations of risk behaviours were as follows: alcohol and smoking, physical activity and smoking, and diet and smoking (Meader et al., 2016, Noble et al., 2015, McAloney et al., 2013). The review findings concluded that among general adult populations, alcohol misuse and smoking was the most commonly identified risk behaviour cluster (Meader et al., 2016). Among young adults, there was consistent evidence of clustering found between sexual risk behaviour and substance misuse (Meader et al., 2016). Moreover, socio-economic status was the strongest predictor of engaging in multiple risk behaviours, which several studies showed that health-risk behaviours in adulthood are predicted by life-course characteristics such as originating from a family in a low socio-economic position, having a low educational level or being in a low socio-economic position as an adult (Meader et al., 2016, Hair et al.). Modifying multiple unhealthy behaviours was suggested by previous RCTs to be more effective than single-targeted behaviour changes (Prochaska et al., 2012, Kruger et al., 2014, Schulz et al., 2014).

1.2 Burden of disease related to alcohol consumption

Alcohol use disorder is recognised as a worldwide public health concern (Whiteford et al., 2013). The WHO reported in the Global status report on alcohol and health in 2012 that about 3.3 million deaths or 5.9% of all global deaths were attributable to alcohol (WHO, 2014). There are significant sex differences in the proportion of global deaths attributable to alcohol, e.g. in 2012, 7.6% of deaths among males and 4.0% of deaths among females were attributable to alcohol. The high levels of alcohol consumption and drinking patterns (e.g. binge drinking) likely have a causal impact on the mortality and morbidity related to many diseases (Grant et al., 2009, Jones and Bellis, 2014, Jones et al., 2008, Kendler et al., 2016, Rehm and Roerecke, 2013, Roerecke and Rehm, 2013). There are a wide range of

diseases and injuries associated with alcohol consumption as defined by the WHO ICD-9 and ICD-10 codes (Appendix 1). In 2010, the impact of alcohol use disorder was also the global leading cause of premature death - equivalent to 8.6 million years of life lost (YLLs) attributable to mental and substance use disorders as illustrated in Figure 1-2 (Whiteford et al., 2013). The largest burden of disease related to alcohol use disorders occurred at age 25-50 years - approximately 2 million disability-adjusted life years (DALYs) across these age groups and - gradually declined for older aged (Figure 1-3). Moreover, the data derived from 187 countries as shown in Figure 1-4 is the burden attributable to mental and substance use disorders as a proportion of all disease burden classified by region. Alcohol use disorder's DALYs varied more than 10 time between regions, and the largest proportion of its DALYs was illustrated in Eastern Europe followed by other parts of Europe, Latin America, and Asia.

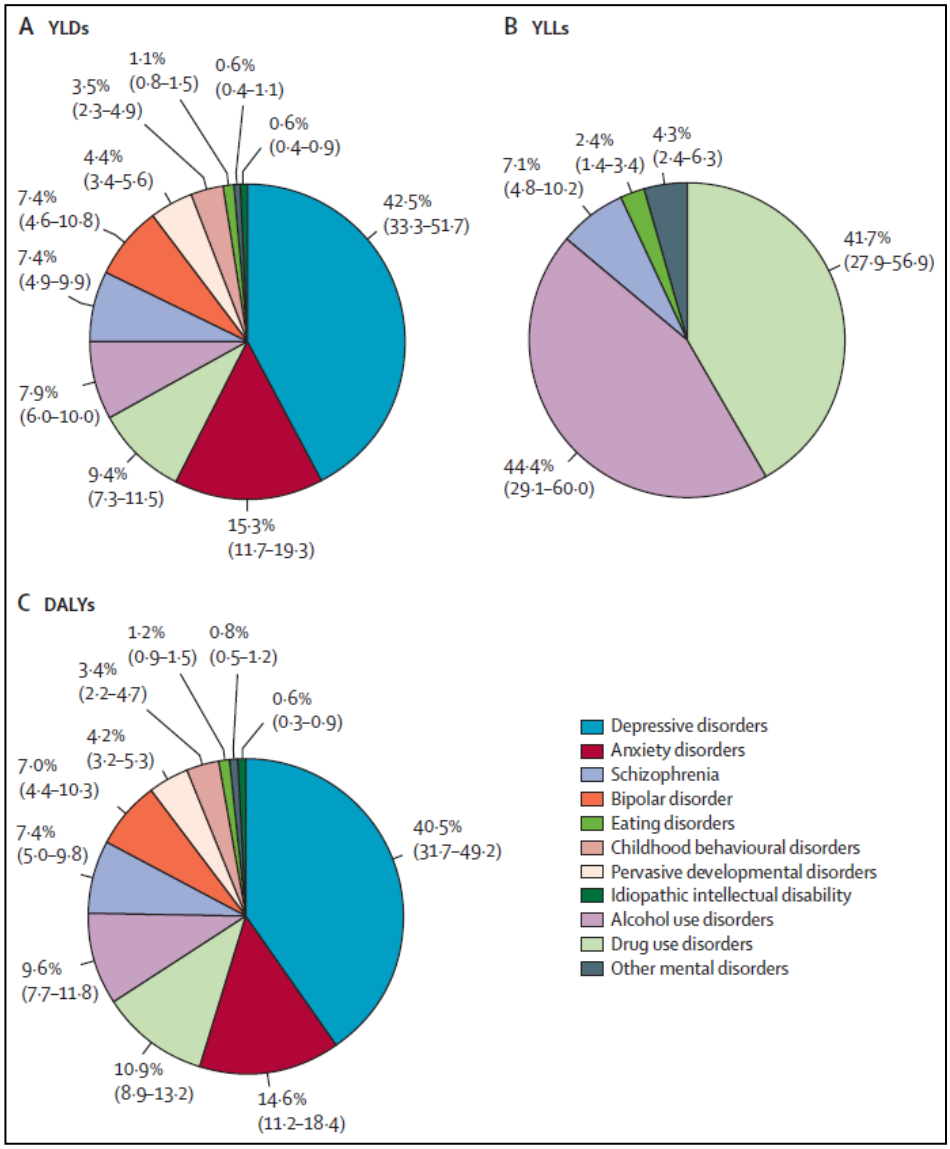


Figure 1-2 Proportion of YLDs (A), YLLs (B), and DALYs (C) as explained by each mental and substance use disorder group in 2010. Data are % (95% CI).

DALYs = disability-adjusted life years. YLDs=years lived with disability. YLLs = years of life lost.

Source: (Whiteford et al., 2013)

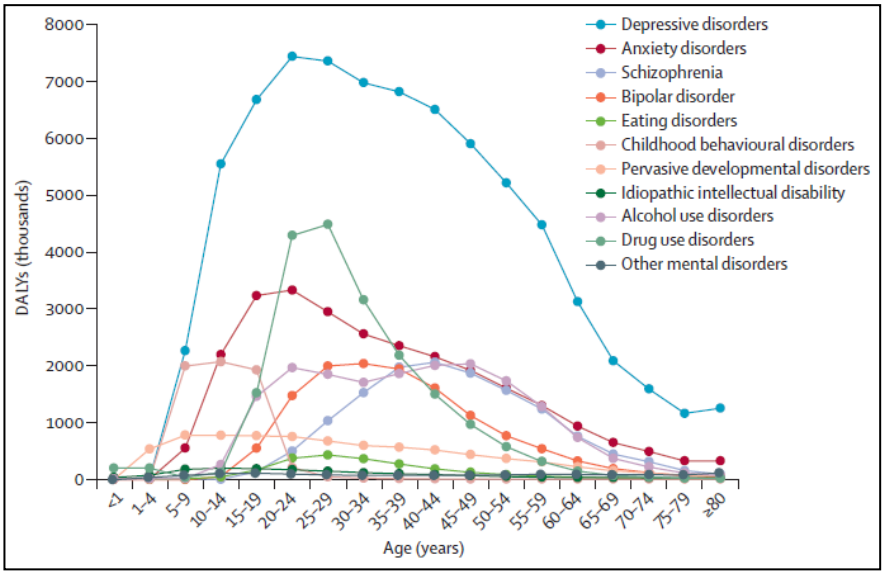


Figure 1-3 Disability-adjusted life years (DALYs) for each mental and substance use disorder in 2010, classified by age.

Source: (Whiteford et al., 2013)

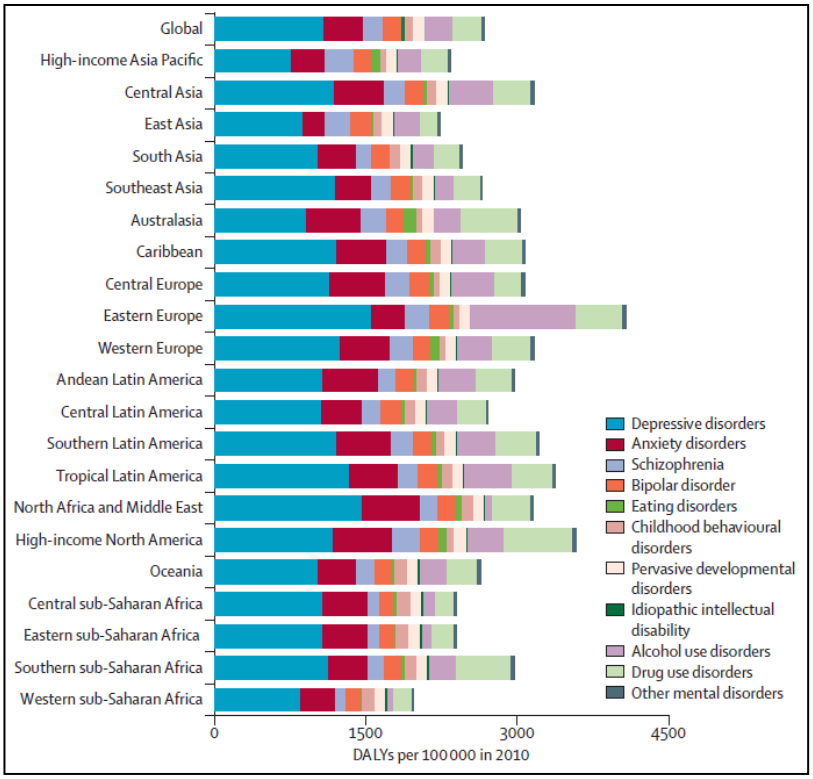


Figure 1-4 Rates of disability-adjusted life years (DALYs) per 100,000 individuals for mental and substance use disorders in 2010, classified by region.

Source: (Whiteford et al., 2013)

1.2.1 Socioeconomic consequences of alcohol use for drinkers

Alcohol use disorders, i.e. alcohol dependence and harmful use of alcohol as outlined in the ICD-10 (WHO, 2007a), is often associated with socioeconomic consequences as shown in Figure 1-1. These consequences include loss of earnings, unemployment, homelessness, poverty, family disruption, and stigmatisation (WHO, 2004, Schmidt et al., 2010). Regarding the stigmatisation of alcohol problems, in a 14-country WHO cross-cultural study of disabilities, key informants assigned "alcoholism" an average rank of 4th out of 18 conditions in terms of the degree of social disapproval or stigma in society - which was a greater disapproval than for having "chronic mental disorder" (Room et al., 2001). Moreover, the effects of stigma often lead to other socioeconomic consequences as mentioned above. For instance, most of the people with alcohol use disorders who were receiving treatment were not in the workforce and did not have a fully stable living situation (Storbjörka and Room, 2008). In addition, alcohol problem drinkers perceived as "drunks" have difficulties obtaining healthcare services since people felt that heavy drinkers should receive less priority in healthcare and contribute to their own illness (Bird et al., 2002, Strong, 1980, Olsen et al., 2003). The economic consequences of expenditures on alcohol are significant, especially in high poverty areas (de Silva et al., 2011). Besides money spent on alcohol, a drinker with alcohol use disorders also suffers other adverse economic effects. These include lowered wages (because of missed work and decreased efficiency on the job), lost employment opportunities, increased medical expenses for illnesses and accidents, legal costs of drink-related offences, and decreased eligibility of loans. Thus, alcohol use disorder may further impoverish the drinker, the drinker's family, or the whole community due to increasing health or social harms (Schmidt et al., 2010).

1.2.2 Alcohol use harms to other individuals

Other individual(s) affected may include a spouse or partner, child, relative, friend, neighbour, co-worker, person living in the same household or a stranger as this is particularly common in the case of traffic accidents. The harms may be relatively mild - such as being awakened by drunken carousers

outside - or may be very severe, including death or a lifelong disability. A number of studies have shown an association between exposure to heavy drinkers and reduced well-being, mental health (e.g. anxiety and depression), and poorer general health status (Casswell et al., 2011a, Dussaillant and Fernandez, 2015, Laslett et al., 2011, Ferris et al., 2011, Livingston, 2009, Livingston et al., 2010, Casswell et al., 2011b).

1.3 Social and economic costs of alcohol use disorder

Alcohol use disorder significantly increases the social and economic costs on society as shown in Table 1-1 (Single et al., 2003). There are two main major categories of alcohol-attributable costs i.e. tangible and intangible costs (WHO, 2009). The tangible costs can be easily measured in money terms and are divided into two types (Single et al., 2003):

1) Direct costs are expenses incurred because of alcohol consumption and related problems. Depending on the society, many of the direct costs are borne by governments. Direct costs attributable to alcohol consumption include healthcare costs, law enforcement costs, and costs of property damage due to traffic accidents. (Thavorncharoensap et al., 2009, Rehm et al., 2009). These estimates are typically derived from registration data of the major institutions of societal response to alcohol use problems such as the healthcare system and the police and criminal justice system (Thavorncharoensap et al., 2009, Rehm et al., 2009). In addition, the direct costs for estimating economic costs of alcohol consumption also include the costs of research and prevention, costs of property damage due to fire and vandalism, and costs of incarceration. However, these costs may lack reliable data in various study settings (Thavorncharoensap et al., 2010).

2) Indirect costs - or lost production - are associated with reduced work time due to morbidity and mortality (WHO, 2009). Indirect costs include the following: 1) cost of premature mortality; 2) cost of reduced productivity, which includes both the cost of productivity loss due to absenteeism and presenteeism (when an employee comes to work but is not productive); 3) cost of loss of employment or early retirement; and 4) costs associated with crime,

i.e. time loss for victims due to crime. These indirect costs are typically borne by society at large because their impact can affect the economic viability of an entire society (WHO, 2014).

The intangible costs are costs assigned to pain and suffering, and more generally related to a diminished quality of life. As much of the efforts of the healthcare system are focussed on the reduction of intangible costs (e.g. pain and suffering), it is apparent that these costs are very important but are difficult to quantify. The most important characteristic of intangible costs is that when they are reduced, e.g. any reduction of pain and suffering, they do not permit a direct transfer of these benefits to any other person regardless of how important the benefit is. An important implication of this characteristic is that there is no market for the benefits of cost reduction as the benefits cannot be bought and sold. Thus, it is extremely difficult to place a value upon intangible costs, and intangible costs are generally not included in economic cost estimation studies (Thavorncharoensap et al., 2009, Single et al., 2003). The contingent valuation method (e.g. willingness-to-pay approach) can be used for valuing intangible costs but there still remain considerable difficulties in its reliability and validity of estimates using this approach (Venkatachalam, 2004).

Table 1-1 Types of social costs attributable to substance abuse

Costs	Private costs (not generally included)	Social costs (generally included in cost estimates)		
	Costs to users	Costs to users and individuals	Costs to federal and other government agencies	Costs to businesses and other private entities
1. Tangible costs				
1.1 Consequences to health and welfare system				
- Treatment for substance abuse	user-paid insurance; out-of-pocket costs	excess insurance premiums	hospital + other health costs	contribution to health insurance
- Treatment for comorbidities and trauma	user-paid insurance; out-of-pocket costs	excess insurance	hospital + other health costs	contribution to health insurance
- Prevention, research, health, and welfare services			research, training, prevention, welfare	corporate research + prevention
1.2 Productivity costs, i.e. consequences to the workplace				
- Premature mortality			forgone taxes	production losses due to premature death
- Lost employment or productivity	forgone income net and taxes	victims' forgone income net of taxes	forgone taxes	workman's company, reduced productivity
1.3 Law enforcement and criminal justice costs				
- Criminal justice response	penalties (e.g. fines)	victim's time	enforcement, court incarceration costs	victim's time (productivity loss); criminal careers
1.4 Other costs, e.g. property destruction				
	unreimbursed property damage	fire losses, accident property damage	accident and fire prevention, fire	fire losses + accident damage to industry
2. Intangible costs (not generally included)				
	pain and suffering to user, quality life years lost	suffering to dependents crime victims + restrictions of public's legal right to expedite		

Source: (Single et al., 2003)

Monitoring social and economic costs is increasingly important as it provides essential information regarding the full social consequences of alcohol consumption at the global and national levels in terms of monetary unit. Thus, a number of studies in many settings have been conducted to estimate the social and economic costs attributable to alcohol consumption and alcohol use disorder (Baumberg, 2006, Bouchery et al., 2011, Jones et al., 1995, Konnopka and Konig, 2007, Laramee et al., 2013, Matzopoulos et al., 2014, Mohapatra et al., 2010, Varney and Guest, 2002, Rehm et al., 2009, Thavorncharoensap et al., 2009, Thavorncharoensap et al., 2010). In the US, the estimated economic cost of excessive alcohol consumption was $223.5 billion in 2006 (72.2% from lost productivity, 11.0% from healthcare costs, 9.4% from criminal justice costs, and 7.5% from other effects) (Bouchery et al., 2011), and binge drinking resulted in costs of $170.7 billion (76.4% of the total costs). In the Republic of South Africa, the estimated total economic cost of harmful use of alcohol was 10-12% of the 2009 gross domestic product (GDP) (Matzopoulos et al., 2014). The direct and indirect costs of morbidity and mortality attributable to alcohol consumption in Germany was estimated at €24.398 billion, or 1.16% of the 2002 GDP (Konnopka and Konig, 2007). Meanwhile, in Scotland, alcohol misuse imposes a substantial burden on society, costing £1.071 billion per year at 2001/2002 prices, and the greatest burden on the individual and society as a whole was arising from lost productivity (Varney and Guest, 2002). At the global level, the economic costs attributable to alcohol in selected high-income (4 countries) and middle-income countries (2 countries) were estimated at 2-2.5% GDP based on the international dollar ($PPP) in 2007, of which indirect cost due to productivity losses was the predominant cost (approximately 70%-80% of total costs) category of all alcohol-attributable social costs (Rehm et al., 2009, Mohapatra et al., 2010).

1.4 Alcohol consumption measurement and under-reporting

Alcohol consumption measurement aims to link consumption with alcohol-related problems such as per capita alcohol consumption compared

with mortality rates over time (WHO, 2014). Thus, it is important to determine consumption as accurately as possible. Measured consumption at the aggregate level (e.g. derived from alcohol sales) is useful in demonstrating links between a large population's consumption and consequences (Robinson et al., 2015). In contrast, individual level alcohol consumption data retrieved from general population surveys have advantages over aggregate level. The volume and patterns of individual alcohol consumption as well as other potentially related characteristics (e.g. socioeconomic status, smoking, and family member drinking) can be measured. Therefore, researchers can link individual alcohol consumption and other characteristics with alcohol-related problems (Dawson, 2003). Moreover, individual level data can be used for comparison of alcohol drinking between population subgroups such as males and females.

A systematic review identified four international guidelines that provide recommendations for measuring alcohol consumption in general population surveys as follows (Nugawela et al., 2016): the International Guide for Monitoring Alcohol Consumption and Related Harm by the WHO (WHO, 2000); the Agreement on ways to measure alcohol consumption by the Kettil Bruun Society (Dawson and Room, 2000) - an international organization of scientists engaged in research on alcohol use and alcohol problems; the Recommended Alcohol Questions by the National Institute on Alcohol Abuse and Alcoholism (NIAAA, 2003); and the Standardized Measurement of Alcohol-Related Troubles Project Guidelines by the European Commission (Moskalewicz and Sierosławski, 2010).

All four guidelines emphasise that surveys measuring alcohol consumption need to contain items on alcohol drinking status (past year and lifetime), average volume of alcohol consumption (past year), and frequency and volume of heavy episodic drinking, where the volume of alcohol is calculated by multiplying the quantity and frequency of relevant drinking occasions over the past year (Moskalewicz and Sierosławski, 2010, NIAAA, 2003, Dawson and Room, 2000, WHO, 2000). For measuring the average volume of alcohol consumption, Beverage Specific Quantity Frequency (BSQF) questions were identified as the most appropriate survey instrument, whereas Quantity

Frequency (QF) questions were identified as adequate when surveys have limited resources and space for alcohol questions. QF questions measure how often alcohol was consumed and how much on each occasion, whereas BSQF questions do the equivalent for different types of alcohol beverage separately. All guidelines recommended Graduated Quantity Frequency (GQF) questions to assess heavy episodic drinking. GQF questions start by asking for the highest level of consumption on any occasion in the past year (alternatively last week) and then, based on the answer, ask a series of follow-up questions on frequency of consuming lesser quantities (e.g. frequency of consuming more than 144, 96, 60, 36 or 24 g of pure alcohol). Moreover, questions about drinking context were also recommended to ask whether participants drank with or without a meal, alone or with others as well as the place of drinking.

Heavy episodic drinking, or binge drinking refers to a drinking pattern of consuming an intensive volume of alcohol over a short period of time that is likely to lead to intoxication and acute consequences (WHO, 2014). According to the WHO, heavy episodic drinking is defined as 'drinking at least 60 g (7.5 units) or more of pure alcohol on at least one occasion in the past 30 days', where 60 g is an approximate cut-off value for high-risk drinking. In the UK, binge drinking is defined as drinking twice or more than the sensible drinking limits of 3–4 units per day for men and 2–3 units per day for women in the last week, where a unit represents about 8 g of ethanol (Lifestyle Statistics of Health and Social Care Information Centre, 2014, Office for National Statistics, 2013, Rutherford et al., 2013a). One unit is equivalent to one shot of a spirit, a glass of wine or half a pint of beer. However, the shorter reference period of last week is likely to greatly underestimate the proportion of heavy drinkers and miss infrequent drinkers (Moskalewicz and Sierosławski, 2010, NIAAA, 2003, WHO, 2000).

The guidelines recommend that total alcohol consumption from surveys should be calculated by combining the average volume of consumption and consumption due to binge drinking occasions (Moskalewicz and Sierosławski, 2010, WHO, 2000). Survey respondents did not normally include heavy drinking occasions in estimates of their average consumption (Stahre et al., 2006).

Therefore, using the average volume of alcohol consumption generated by BSQF questions on its own can contribute towards the underestimation of alcohol consumption in surveys.

The assessment of self-reported alcohol consumption typically indicates deliberate underestimation (ranging from 40% to 60%) compared to per capita sales data (Babor et al., 2010a, Meier et al., 2013, Livingston and Callinan, 2015). This underestimation of self-reported alcohol consumption is likely to occur mainly due to the following reasons: 1) drinking by people outside the sampling frame e.g. under 16 years, homeless, military personnel and prisoners, people in care homes, and university students living in residence halls - some of which are more likely to be involved in heavy drinking (Makela and Huhtanen, 2010, Kelfve and Ahacic, 2015, Meier et al., 2013); 2) drinking non-responders to the survey, e.g. students and dependent drinker, and proxy interviewees (Gorman et al., 2014, Maclennan et al., 2012, Meiklejohn et al., 2012); and 3) under-reporting bias such as selective reporting, recall bias and accidental under-estimation (Boniface and Shelton, 2013, Stockwell et al., 2014, Livingston and Callinan, 2015). In addition, the survey tools themselves and the framing of questions are likely to influence the adequacy of survey measures of alcohol consumption (Dawson, 2003, Bloomfield et al., 2013, Nugawela et al., 2016).

1.5 Alcohol Use Disorder Identification Test (AUDIT)

The AUDIT consists of 10 questions about recent alcohol use consistent with the ICD-10 definitions of alcohol dependence and harmful alcohol use. Once computed, the total score ranges between 0 and 40 (World Health Organization, 1993, Babor et al., 1989). Table 1-2 shows the questions, conceptual domains, item content, and the score ranges of the AUDIT (Babor et al., 2001, Babor et al., 1989). It is conceptualised to have three different domains: 1) quantity and frequency of drinking - which can detect hazardous alcohol use, i.e. average frequency and quantity of drinking - and frequency of six or more standard drinks on one occasion – also known as binge drinking behaviour; 2) possible alcohol dependence symptoms as defined by the WHO

ICD-10 code, i.e. unable to stop, failing normative expectations, and morning drinking; and 3) harmful alcohol use, i.e. guilt, blackout, injury, and concern of others such as the doctor or family members.

Table 1-2 Questions, domains, item content, and the score ranges of the Alcohol Use Disorders Identification Test (AUDIT)

Questions	0	1	2	3	4
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more
3. How often do you have six or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	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?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
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?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year
10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking last year?	No		Yes, but not in the last year		Yes, during the last year

Domain	Question	Item content
Hazardous alcohol use	1	Frequency of drinking
	2	Typical quantity
	3	Frequency of heavy drinking
Possible alcohol dependence symptoms	4	Impaired control over drinking
	5	Increased salience of drinking
	6	Morning drinking
Harmful alcohol use	7	Guilt after drinking
	8	Blackouts
	9	Alcohol-related injuries
	10	Others concerned about drinking
Total score		

1.5.1 Use of the AUDIT in the healthcare setting

The AUDIT has been recommended as a screening tool for detecting problematic alcohol use in the healthcare setting, and it has been recommended for screening and treatment of alcohol use disorders in the primary healthcare setting in the UK and many other countries (National Collaborating Centre for Mental Health, 2011, Dybek et al., 2006, Gache et al., 2005, Li et al., 2011). It has also been recommended for use for the same purpose in other settings, e.g. emergency departments (Neumann et al., 2004) and outpatient departments in hospitals (Pradhan et al., 2012, Obadeji et al., 2015). The WHO guidelines for interpreting AUDIT scale scores are as follows (Babor et al., 2001):

- 0 to 7: low-risk drinking behaviour, or abstinence;
- 8 to 15: medium level of alcohol problems, with increased risk of developing alcohol-related health or social problems (sometimes described as hazardous drinking behaviour);
- 16 to 19: high level of alcohol problems, for which counselling is recommended (harmful drinking behaviour);
- 20 or above: warrants further investigation for possible alcohol dependence.

Furthermore, from reviews of both English and non-English studies of the AUDIT's performance characteristics, the standard value of 8 consistently yielded lower sensitivities and higher specificities for women than for men in detecting alcohol misuse (Reinert and Allen, 2007, Gache et al., 2005, Aalto et al., 2009, Neumann et al., 2004, Dybek et al., 2006). These studies concluded that the cut-off points for effective detection of alcohol use disorder in women need to be lower than the original recommended value of 8. The optimal cut-off points were found to be ≥ 8 for males (sensitivity range of 0.75-0.80 and specificity range of 0.81-0.94) and ≥ 5 for females (sensitivity range of 0.76-0.96 and specificity range of 0.81-0.95) (Reinert and Allen, 2007). Thus, the current study applies the new recommendations to categorise the AUDIT score using different cut-offs between males and females as follows:

- 0 to 7 for males and 0 to 5 for females: low-risk drinking behaviour, or abstinence;
- 8 to 15 for males and 6 to 12 for females: medium level of alcohol problems, with increased risk of developing alcohol-related health or social problems (sometimes described as hazardous drinking behaviour);
- 16 to 19 for males and 13 to 16 for females: high level of alcohol problems, for which counselling is recommended (harmful drinking behaviour);
- 20 or above for males and 17 or above for females: warrants further investigation for possible alcohol dependence.

1.5.2 Use of the AUDIT in general population surveys

Although the AUDIT was originally developed for use in the primary healthcare setting, it has also been applied for estimating alcohol use disorder prevalence in general population surveys as a means of supporting policy-making (Aalto et al., 2009, Knibbe et al., 2006, Assanangkornchai et al., 2010). Three validation studies of the AUDIT in general population surveys were conducted in Sweden (Lundin et al., 2015), Germany (Rumpf et al., 2002), and the US (Dawson et al., 2005); in the US study, an abbreviated version of the AUDIT was used, or AUDIT-C. These studies compared the AUDIT to the fourth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) - the gold standard for diagnosing alcohol misuse, alcohol dependence, and at-risk drinking (American Psychiatric Association, 1994). The results showed the agreeability between the DSM-IV and the AUDIT, which was measured by the area under the receiver operator characteristic curve (ROC). In the general population sample, the AUDIT and AUDIT-C showed outstanding discrimination for alcohol dependence (area under ROC>0.9), and excellent discrimination for alcohol use disorder (area under ROC between 0.85-0.92) and at-risk drinking (area under ROC between 0.80-0.86) (Lundin et al., 2015, Rumpf et al., 2002, Dawson et al., 2005). Using the WHO recommended cut-off AUDIT score of 8, the AUDIT showed low sensitivity for alcohol misuse (0.37) but specificity was high (0.94) (Rumpf et al., 2002). For using different cut-offs of alcohol use disorder between men (AUDIT score of 6 or 7) and women (AUDIT score of 4 or 5), there was a higher range for sensitivity from 0.71-0.79 for men and 0.66-

0.74 for women but specificity was at a slightly lower range from 0.77-0.82 for men and 0.82-0.83 for women (Dawson et al., 2005, Lundin et al., 2015). In conclusion, the findings of the validation studies suggest that not only can the AUDIT be used for identifying alcohol use disorders in healthcare settings but it can also be used in measuring alcohol use disorders in general population settings.

A recently published systematic review and meta-analysis examined the association of alcohol use disorders and all-cause mortality (Roerecke and Rehm, 2013). The study compared the mortality risk of alcohol use disorder and non-alcohol use disorder differentiated by sex and age. Moreover, the meta-analysis performed a subgroup analysis by studying the population that had alcohol use disorders identified from the clinical setting and those identified from the general population survey. The results showed that alcohol use disorder in the clinical setting had higher mortality risk than those in the general population. In men, the relative risk (RR) among clinical samples was 3.38 (95% confidence interval (CI): 2.98-3.84); in women, RR was 4.57 (95% CI: 3.86-5.42). For the general population surveys, the RR of alcohol use disorder mortality was lower at 1.91 (95% CI 1.51-2.42) in men; however, no data were available for women. Presumably, high-risk drinkers in the clinical setting who seek treatment might have more severe conditions compared to those with untreated alcohol use disorder in the general population. Unfortunately, due to insufficient data available for the survey population, stratified analyses based on grouped age, sex, and different follow-up period could not be performed (Fichter et al., 2011, Perala et al., 2010, Min et al., 2008, Ojesjo et al., 1998, Dawson, 2000, Neumark et al., 2000).

In particular, these eligible survey studies contained various measurements of identifying alcohol use disorder depending on the country settings. Each setting selected their own validated questionnaire for the alcohol consumption population survey such as the Composite International Diagnostic Interview (CIDI) (Kessler and Ustun, 2004), the Munich Alcoholism Test (MALT) (Feuerlein et al., 1977), the Severity of Alcohol Dependence Questionnaire (SADQ) (Stockwell et al., 1983) or the Michigan Alcoholism Screening Test

(MAST) (Selzer, 1971). The alcohol use disorder results reported in these studies might not have been the same, leading to heterogeneity between studies – shown by high heterogeneity where a pooled result was performed (p-value of heterogeneity<0.001 and I^2=88.1). Furthermore, there was no eligible study using the AUDIT for identifying alcohol use disorders which was included in the meta-analysis. As a result, evidence is scarce on the use of the AUDIT for alcohol misuse assessment in the general population. Moreover, there is no evidence that reveals an association between the measured AUDIT score and alcohol-related consequences (e.g. mortality and morbidity) in national representative samples.

1.6 Effectiveness and cost-effectiveness of alcohol interventions

Alcohol interventions can be evaluated in two terms: effectiveness and cost-effectiveness. Effectiveness is defined as a measure of the extent to which a specific policy, programme or intervention, when deployed in the real world, does what it is intended to do for a specified population. Meanwhile, cost-effectiveness is defined as an economic evaluation that compares the costs of two or more interventions with differences in one single measure of outcome. The general principles on which particular alcohol interventions work are fairly well understood and can often be applied across societies. This section summarises effectiveness and cost-effectiveness of alcohol interventions:

1.6.1 Provision of information and education

The provision of information and education on alcohol-related harms and alcohol interventions is important to raise awareness and impart knowledge. Providing information and education particularly in an environment in which many competing messages are received in the form of marketing and social norms supporting drinking, and in which alcohol is readily accessible - does not lead to sustained changes in alcohol-related behaviour (WHO, 2007b). Moreover, systematic reviews have shown that school-based interventions (e.g. classroom-based programmes, combined classroom-based with family-based

and/or community based intervention components, and other approaches delivered outside of lesson time including brief interventions and peer support programmes) lack clear evidence on which types of programmes are most effective based on effectiveness reviews (Jones et al., 2007, Petrie et al., 2007). In addition, long-term follow-up data were not available for the majority of programmes so it is difficult to determine the value of school-based interventions in terms of longer-term impacts of adolescent alcohol use as there is no clear evidence to determine the relationship between alcohol use in adolescence and adulthood (Jones et al., 2007).

Moreover, there was a lack of economic evaluation studies in the field potentially due to insufficient effectiveness data e.g. students reporting hazardous/harmful drinking and data on alcohol-related outcomes in young people such as injuries, violence and disorder, unintended pregnancies, and school attendance. Media advocacy can lead to a reframing of the solution to alcohol-related problems, which is a coordinated approach by relevant sectors, and results in increased attention to alcohol within political and public agendas (Babor et al., 2003). In addition, social marketing interventions are associated with changes in alcohol-related behaviour; however, a recent systematic review concluded that it was inconclusive whether applying the principles of social marketing in alcohol prevention interventions was indeed effective in changing this behaviour (Janssen et al., 2013). However, public information campaigns have been found to be ineffective in reducing alcohol-related harms (Babor et al., 2010a). Exceptions for this are mass media campaigns to reduce drinking and driving, for which systematic reviews and economic evaluation studies have found them to be effective and cost-effective when implemented in the presence of strong drinking and driving countermeasures (Cobiac et al., 2009, Ditsuwan et al., 2013, Doran et al., 2008, Elder et al., 2004, Yadav and Kobayashi, 2015).

1.6.2 Community-based programmes

Two literature reviews reported multi-component community-based interventions for controlling accessibility – including the environmental

contexts of selling, encourage responsible retailing, involved enforcement of public health polices for drinking and driving, manage licensed premises and their surrounding environments and better enforce alcohol legislation – can reduce high-risk alcohol consumption and alcohol-related injuries resulting from motor vehicle crashes and assaults (Giesbrecht, 2003, Jones et al., 2011). In addition, a longitudinal time series analysis explored the impacts of a combination of communities and media mobilisation, responsible beverage service, strengthened licensing legislation, increased enforcement of the ban on sales of alcohol to under-age customers and of drink-driving, and licensing legislation (Holder et al., 2000). The combined interventions were associated with reductions in alcohol consumption, assaults, and road traffic accidents.

Only one cost-effectiveness study was found that was about a larger community-based programme called Stockholm prevents Alcohol and Drug problems (STAD). Essentially, it studied community mobilisation which aimed to increase awareness of the problems associated with alcohol consumption; conducted a two-day responsible beverage service training course for servers, doormen, and restaurant owners; and increased enforcement of alcohol laws (Wallin and Andreasson, 2004, Wallin et al., 2005, Wallin et al., 2003, Warpenius et al., 2010). The STAD programme was found to have been effective and cost-saving (Mansdotter et al., 2007). However, the uncertainty analysis was restricted to the impact of the low response rate to the survey.

1.6.3 Workplace intervention

The workplace offers advantages as a setting for interventions that result in primary prevention of alcohol abuse. Such programmes have the potential to reach broad audiences and populations that would otherwise not receive prevention programmes, and thereby benefit both the employee and employer, e.g. reduction of sickness absence and unemployment, and lost outputs due to early death (Ames and Bennett, 2011). A systematic review of workplace interventions for alcohol-related problems identified a wide range of interventions (Webb et al., 2009). Most of studies conducted in the US consisted of psychosocial skills training; brief interventions including feedback of results

of self-reported drinking, lifestyle factors, and general health checks; and alcohol education delivered via an Internet website. The psychosocial interventions included peer referral, teambuilding, stress management, and skills derived from the social learning model. Ultimately, there were variations of self-reported alcohol consumption measurements among included studies (Webb et al., 2009). In addition, two systematic reviews focussed on the effects of alcohol and drug abuse screening at the workplace for preventing injury or work-related effects such as sickness absence related to injury (Cashman et al., 2009, Pidd and Roche, 2014). Most of the studies reported significant reductions in alcohol consumption, alcohol-related problems, and occupational accident or injury rates. However, the reviews raised some methodological problems of the individual studies, e.g. allocation bias, a lack of exposure to the intervention, contamination of the intervention due to change in work-place policies, and a lack of reliance on self-reported alcohol drinking over the follow-up period (Webb et al., 2009, Cashman et al., 2009, Pidd and Roche, 2014).

There is still a limited number of cost-effectiveness studies for workplace interventions. Only one cost-benefit analysis was shown to have cost-savings from reduction in the injury rate of peer-based workplace substance abuse (e.g. alcohol abuse) in a US transportation company (Miller et al., 2007). In addition, a cost-benefit modelling study of an alcohol intervention in the UK quantified a monetary valuation of workplace harms, which includes absence due to sickness and unemployment combined with other harms caused by alcohol consumption, i.e. health and crime (Brennan et al., 2014a). However, this study did not only focus on workplace interventions but also applied the model for macro-level interventions.

1.6.4 Addressing the availability of alcohol

A greater density of alcohol outlets was found to be associated with higher alcohol consumption leading to harms caused by alcohol drinking such as assault, homicide, child abuse and neglect, self-inflicted injury, and road traffic accidents (Huckle et al., 2008, Hughes et al., 2011, Roche et al., 2013). Thus, many countries implemented policies related to availability of alcohol,

e.g. hours and days of sales and change in alcohol outlet density – which is measured as the number of licenses per kilometre of roadway (Campbell et al., 2009, Fone et al., 2016, Livingston et al., 2007, Popova et al., 2009). The policies led to fewer alcohol-related problems, including homicides and assaults (Duailibi et al., 2007). There are also widely dispersed bans on the use of alcohol in particular locations and circumstances, such as drinking in parks or streets, hospitals or at the workplace (Babor et al., 2010a). Public monopolies on the sale of alcohol can also reduce alcohol-related harms (Holder et al., 2008, Babor et al., 2003). Such systems tend to have fewer outlets open for shorter hours than private retailers. An implementation of laws that set a minimum age for the purchase of alcohol ranging typically from aged 16 to 20 years, in conjunction with enforcement of the alcohol sellers (Grube and Stewart, 2004), show a reduction in alcohol-related harms and drink-driving casualties (Wagenaar and Toomey, 2000).

For cost-effectiveness evidence, licensing controls - including hours of operation for outlets selling alcohol, types of outlet permitted to sell alcohol, density of outlets within an area, and age at which alcohol can be legally purchased or consumed - were a cost-effective intervention in the Australian and Danish contexts (Doran et al., 2008, Holm et al., 2014b). In addition, the UK modelling study also showed that outlet density and licensing hour policies are able to reduce both alcohol consumption and alcohol-related harms in term of monetary unit; however, ICER was not reported due to the lack of information about intervention costs (Purshouse et al., 2009).

1.6.5 Addressing the marketing of alcoholic beverages

Alcohol advertising is one of the many factors that have the potential to encourage young people to drink. Two of the most recent systematic reviews reported an association between alcohol marketing (e.g. alcohol promotion (mainly advertising), product attributes, and place of sale/availability) and drinking behaviours among young people (under legal drinking age) including drinking initiation, continuation, frequency, and intensity (Scott et al., 2017, Jernigan et al., 2017). The reviews consistently found evidence of a positive

association between the level of marketing exposure and level of youth alcohol consumption, i.e. initiation of alcohol use for the exposure group (OR 1.00 - 1.69) and subsequent binge or hazardous drinking (OR 1.38 - 2.15) (Jernigan et al., 2017). The expectancies of young people who have not started to drink are influenced by normative assumptions about teenage drinking as well as through observation of drinking by parents, peers, and models in the mass media (Anderson et al., 2009b, Rossow et al., 2016, Leung et al., 2014). A number of RCTs and interrupted time series studies of restricting alcohol during the control period or banning alcohol advertising (partial or full) to reduce alcohol consumption in adults and adolescent were reviewed, but the evidence was determined to be very low quality due to a high risk of bias, serious indirectness of study population, and serious level of imprecision in the results (Siegfried et al., 2014). Thus, there was a lack of robust evidence for recommending or discouraging against or recommended the implementation of these inventions for alcohol advertising.

Although the effectiveness of alcohol advertising bans remains unclear, two cost-effectiveness models assumed that if advertising increases consumption, and if a set of certain media bans on alcohol advertisement (via billboards, television, radio, etc.) reduces total advertising, then advertising bans will have a negative effect on alcohol consumption by an applied 4-6.5% g/day reduction in consumption of the entire population (Cobiac et al., 2009, Holm et al., 2014b, Chisholm et al., 2004). The alcohol advertising bans was shown to be cost-saving. For the UK study, there was a disagreement in the literature concerning whether advertising bans (in the absence of other legislation) reduces alcohol consumption or increases it by having the unintended side-effect of increased price competition between competitors, so the effects of a complete ban in alcohol advertising estimated an overall change in consumption ranging from –26.9% to +4.9%, and a financial value of accumulated harm avoided over 10 years ranging from a gain of £33.5bn to a loss of £7.1bn (Purshouse et al., 2009). These figures can present the need for further research on alcohol advertising impacts.

1.6.6 Drink-driving policies

Drink-driving policies – such as the setting of a blood alcohol concentration (BAC) level, and intensive random breath-testing - do reduce alcohol-related injuries and fatalities (Babor et al., 2010a). In these scenarios, police regularly stop drivers on a random basis to check their BAC level, and establish checkpoints where all cars are stopped and drivers suspected of drink–driving are breath-tested. The majority of the lower limit introduced and evaluated is ranged from 0.2 - 0.8 g/litre (Shults et al., 2009, Shults et al., 2001, Fell and Voas, 2006). However, the results from reducing BAC levels found that lowering BAC levels combined with law enforcement in practice by utilising random checks on the road could reduce alcohol-related crashes, fatalities or injuries (Albalate, Andreuccetti et al., 2011, Chang et al., 2012, Fell and Voas, 2006, Sebego et al., 2014). A difference of a time lag (range from 1 to 5 years) to observe the effectiveness among countries was shown because the results may have been affected by time when aggressive policies and other activities (e.g., education, enforcement) were implemented (Albalate, Andreuccetti et al., 2011, Fell and Voas, 2006, Sebego et al., 2014).

A meta-analysis of nine research studies of sufficient design quality and level of implementation found that laws setting a legal BAC level of 0.8 g/litre resulted in a median reduction of 7% in alcohol-related motor vehicle fatalities, and unrestricted and selective breath-testing resulted in fewer accidents thought to have involved alcohol (Shults et al., 2001). Moreover, many alcohol policies can reduce alcohol-related road traffic fatalities including higher prices for alcohol, minimum purchase age laws, controls over the density of outlets, promotion and advertising of alcohol, and opening hours of sales and outlet density, and mass media campaigns supporting drink-driving policies (Grube and Stewart, 2004). An economic evaluation of a drink-driving policy was found to be very cost-effective due to preventing premature death and harms to accident victims (Cobiac et al., 2009, Ditsuwan et al., 2013).

1.6.7 Screening and brief intervention

Alcohol screening and brief intervention (SBI) is the most effective evidence-based treatment (Babor et al., 2010b, Babor et al., 2007). Systematic reviews and meta-analyses of the effectiveness of SBIs for hazardous and harmful alcohol consumption have been found to have a positive impact on alcohol consumption, mortality, morbidity, alcohol-related injuries, and alcohol-related social consequences (Kaner et al., 2009, Mdege et al., 2013, Angus et al., 2014a). SBI policies have been examined in many setting such as primary care, accident and emergency units, workplaces, and community pharmacies (Barbosa et al., 2015, Angus et al., 2014a, Alvarez-Bueno et al., 2015, Elzerbi et al., 2015).

Primary healthcare is the most extensively studied setting for the evaluation of SBIs, and these studies consistently reported that SBIs could reduce hazardous and harmful consumption at 6 months and 12 months (Alvarez-Bueno et al., 2015, Elzerbi et al., 2015). For SBIs in emergency departments, a meta-analysis reported that it was effective at reducing mean weekly alcohol consumption at 6 months and 12 months (Elzerbi et al., 2015, Schmidt et al., 2016). Workplace SBIs were effective but it is not clear for which type of employee SBIs may be most beneficial for (Schulte et al., 2014); furthermore, employees may be anxious about the potentially negative consequences of self-disclosing heavy drinking to their employer. A literature review found little empirical support for the effectiveness of SBI in community pharmacies (Watson and Blenkinsopp, 2009); the evidence showed a possibility that pharmacists were undertrained in the delivery of SBIs.

In term of cost-effectiveness, SBIs is considered as cost-effective, and several examples are estimated as being cost-saving (providing additional health benefits and reducing health service costs overall) when compared against a ‘do nothing’ option (Purshouse et al., 2013, Holm et al., 2014b, Doran et al., 2008, Cobiac et al., 2009).

1.6.8 Pricing policies

Drinkers respond to changes in the price of alcohol as they do to changes in the prices of other consumer products. When other factors such as income and prices of other goods are held constant a rise in alcohol prices leads to less alcohol consumption and less alcohol-related harms in many settings (Gallet, 2007, Wagenaar et al., 2009, Pan et al., 2006, Parry et al., 2003). A meta-analysis of 132 studies found that the impact of an increase in alcohol price tends to be stronger in the longer- rather than the shorter-term – as shown by a median price elasticity for all beverage types of -0.52 in the short-term and -0.82 in the long-term (Gallet, 2007). An elasticity of -0.52 means that for every 10% increase in price, consumption would fall by 5.2%.

Another meta-analysis of 112 studies found mean price elasticities for beer to be -0.46, -0.69 for wine, and -0.80 for spirits (Wagenaar et al., 2009). If prices are raised, consumers reduce their overall consumption and tend to shift to cheaper beverages, with heavier drinkers tending to buy cheaper products within their preferred beverage categories (Gruenewald and Treno, 2000). Therefore, influencing prices of the cheapest drinks on the market by raising floor prices has a larger impact on total consumption than increasing the prices of more expensive drinks (Gruenewald and Treno, 2000). Moreover, increasing the price of alcohol through taxes also showed potential to reduce health inequalities (Meier et al., 2016, Holmes et al., 2014a). Low SES groups tend to drink less but are more likely to suffer from alcohol-related harms than less-deprived people; defined as the Alcohol Harm Paradox (Smith and Foster, 2014). As such, this might have a greater financial impact on alcohol expenditure when alcohol price increases, leading to a reduction of alcohol consumption as well as alcohol-related harms (Meier et al., 2016, Holmes et al., 2014a).

A systematic review on public policies affecting the price of alcoholic beverages suggested that doubling the alcohol tax would reduce alcohol-related mortality by an average of 35%, traffic crash deaths by 11%, sexually transmitted disease by 6%, violence by 2%, and crime by 1.4% (Wagenaar et al.,

2010). Economic modelling studies have predicted that taxation and pricing policy (e.g. minimum unit pricing) leads to large gains in health and life expectancy. In addition, these policies have been a cost-effective approach to preventing alcohol-related harms and increasing health outcome gained, even though these studies were conducted in different settings and used different methodological approaches (Angus et al., 2015, Doran et al., 2008, Holm et al., 2014b, Byrnes et al., 2010, Stockwell et al., 2012).

1.7 Methodological issues of effectiveness and cost-effectiveness evaluation of public health interventions

Since most of public health interventions involve complex multi-levels of components, i.e. the policy, environment, and individual levels, evaluating these interventions requires evidence beyond efficacy trials to measure the potential impacts of the interventions, especially in real-world settings (Koorts and Gillison, 2015, Thomas et al., 2014). An intervention that works well in a given setting may be ineffective elsewhere, presenting a huge challenge to international health recommendations (Victora et al., 2004). While the interventions and outcomes of clinical medicine operate at the biomedical level, the outcomes of public health interventions do not always occur at the same operational level as the intervention. In other words, the outcomes of some interventions operating at the individual level (e.g. provision of information and education) can appear at the population level (e.g. social norms) (Jones et al., 2007, Petrie et al., 2007). Similarly, some interventions operating at the population level such as legislation and mass media campaigns can have effects at the individual level (e.g. service provision, changes in behaviour or knowledge) (Janssen et al., 2013, Fell and Voas, 2006).

1.7.1 Evaluation of public health intervention effectiveness

The assessment of causality for public health interventions has been a persisting controversy in term of the reliance on the study design as the main criterion for the credibility of evidence (Rychetnik et al., 2002). An

experimental design as RCT is suggested to be conducted, because it is the most robust method of preventing bias (Craig et al., 2008). If either individually or cluster randomised trials are not appropriate due to practical or ethical objections to experimentally evaluating, other experimental design for evaluating complex interventions should be considered as follows (Craig et al., 2008):

- *Stepped wedge cluster designs (Hemming et al., 2015)* — This design involves a random and sequential crossover of clusters from control to intervention until all clusters are exposed. Observations are made during a baseline period (before any cluster is randomised to receive the intervention) and again in a post-intervention period (where clusters randomised to the intervention have switched to receiving the intervention). It allows a trial to be conducted without delaying roll-out of the intervention. Eventually, the whole population receives the intervention but with randomisation built into the phasing of implementation.

- *Preference trials and randomised consent designs* — Practical or ethical obstacles to randomisation can sometimes be overcome by using non-standard designs. When patients have strong preferences among treatments, basing treatment allocation on patients' preferences or randomising patients before seeking consent may be appropriate.

- *N of 1 designs* — Conventional trials aim to estimate the average effect of an intervention in a population. N of 1 trials, in which individuals undergo interventions with the order or scheduling decided at random, can be used to assess between and within person change and to investigate theoretically-predicted mediators of that change.

If an experimental approach is not feasible, because the intervention is irreversible, applies to the whole population by necessity, or because large scale implementation is already under way, a quasi-experimental or an observational design may be considered. Moreover, resources for public health

research and evaluation are scarce, so more attention must be given to assessing the cost and feasibility of various study designs despite the investment of RCTs relative to public health intervention effectiveness in producing data sufficient for sound decision-making.

For evaluating effectiveness of large-scale public health interventions, there are three broad types of evaluations: process, impact, and outcome (Round et al., 2005). Firstly, process evaluation is used to assess the elements of intervention development and delivery. Process evaluation will usually aim to capture fidelity (whether the intervention was delivered as intended) and dose (the quantity of intervention implemented) (Moore et al., 2015). In a feasibility and piloting phase after an intervention has been developed, process evaluation will focus on the quality and appropriateness of the materials and approaches used (Round et al., 2005). In the implementation stage, process evaluation can be useful in tracking the reach of the intervention (whether the intended audience comes into contact with the intervention and how) and the level of implementation of all aspects, and in identifying potential or emerging problems (Round et al., 2005). Process evaluations may test hypothesised causal pathways using quantitative data as well as using qualitative methods to better understand complex pathways or to identify unexpected mechanisms (Bonell et al., 2012).

Secondly, impact evaluation is used for the assessment of intermediate effects, and can therefore be used at the completion of implementation stages (Round et al., 2005). Impact evaluation may also determine what interventions are worthy of sustained investment and for identifying those that work in real-world settings. A widely-used impact evaluation framework is the RE-AIM framework. It consists of five dimensions, namely Reach, Effectiveness, Adoption, Implementation and Maintenance (Glasgow et al., 2006, Glasgow et al., 1999, Harden et al., 2015). Impact evaluation assesses the degree to which programme objectives were met, e.g. changes in health literacy, behaviours or behavioural intentions, social action, service delivery, organisational change, environmental change or policy development (Round et al., 2005).

Lastly, outcome evaluation is applied for measurement of the longer-term effects of interventions and is related to assess whether a programme's goal has been achieved (Round et al., 2005). The long-term effects may include reductions in incidence or prevalence of health conditions, changes in mortality, sustained behaviour change, and improvements in quality of life. The outcome evaluation has been an important challenge for public health intervention evaluations due to the context of such intervention, particularly the multifaceted, complex, and long-term nature of anticipated programme benefits; and the shortage of sensitive or suitable outcome measures (Weatherly et al., 2009).

Evaluation designs include quantitative designs - which rely on a collection of numerical data (e.g. pre/post surveys, with or without a comparison group, and trend analysis), and qualitative designs - which rely on a collection of written or spoken data (e.g. interviews, focus groups, case studies, document analysis, and participatory action research) (Round et al., 2005). Quantitative designs are frequently used to measure impacts while qualitative designs are useful in process evaluation; however, this distinction is not definitive. Frequently, impact evaluation will look for differences in the target group or community setting before and after the programme, and sometimes seek to compare this with a 'control group' that did not take part in the programme. It is not always appropriate, or financially feasible, to conduct such experimental research in the evaluation of integrated health promotion, where the effect of the program in the intervention group is compared to a control group. However, practitioners should try to ensure their evaluation designs are rigorous. This involves using validated tools where possible and using triangulated evaluation designs (where a range of evaluation methods is incorporated).

1.7.2 Economic evaluation of public health intervention

Economic evaluations of public health interventions have been gaining increasing attention from public health policy-makers. An economic evaluation is defined as a tool to compare the costs and benefits of alternative

interventions, treatments or policy options. Even though the principles and methodological guidelines of clinical interventions have been well-established, there have been challenges in applying those guidelines for the economic evaluation of public health interventions (Briggs et al., 2006c, Drummond MF et al., 1997, Gray et al., 2011a, ISPOR, 2014, NICE, 2013, Chaikledkaew and Kittrongsiri, 2014, Teerawattananon and Chaikledkaew, 2008). The most challenging aspects of applying the principles of cost-effectiveness analysis for public health evaluations were identified in the public health context from the policy-maker's perspective (Chalkidou et al., 2008, Lorgelly et al., 2010). These include:

- *Measuring benefits:* the use of quality adjusted life years (QALYs) (and EQ-5D) and the possible need for evaluations to have more than one outcome measure;
- *Public versus individual:* the role of individual choice in population-based interventions, and how to account for any resulting externalities;
- *Equity versus efficiency:* public health programmes frequently target health inequalities such that the issue of weighting outcomes may need to be addressed together with other distributional concerns;
- *Perspective:* the perspective for public health evaluations has been broadened to include the public sector, and this may lead to inconsistencies when making comparisons with clinical interventions;
- *Extrapolation:* defining the appropriate time horizon and how meaningful such extrapolations will be in the absence of robust evidence;
- *Quality of evidence:* the evidence base is weaker in public health, and controlled trials are often impossible;
- *Cost effectiveness threshold:* whether the same threshold should be applied to both clinical and public health interventions.

Moreover, a more rigorous assessment of the issues for applying standard economic analysis techniques to public health evaluations has also been undertaken (Weatherly et al., 2009). Weatherly et al. identified four main

methodological challenges and recommendations for the cost-effectiveness analysis of public health interventions as follows:

1) Attribution of effects: Compared to healthcare interventions, it would require different approaches to estimate the costs and outcomes of public health interventions while avoiding biased estimates. RCTs can be conducted to assess the intervention effects and measured within-trial or short-term effect, while the effects of public health programme often become noticeable many years after implementation. As a result, the key challenges were how to best obtain true estimates of effect, what the existing literature can offer by way of evidence, how primary research can generate quality evidence, and defining the appropriate time frame within which to measure success (Lorgelly et al., 2010). Hence, conducting RCTs should be a source of evidence on relative effectiveness when evaluating public health interventions' effectiveness, where possible.

However, the extrapolation of outcomes beyond the end of the trial should be considered, and the outcome measured should match between within-trial and available in longer-term observational studies. Where RCTs cannot be undertaken, gaps in the evidence-base may be filled through data from natural experiments and non-experimental data. In analysing data used for economic evaluations, all relevant evidence should be considered including the evidence synthesis of different study designs. Furthermore, econometric approaches can be employed for analysing non-experimental data (Blundell and Dias, 2000), and these include various matching techniques such as propensity scores, difference in differences techniques, synthetic controls method, time-series analyses of natural experiments, and, where appropriate, more sophisticated econometric modelling and structural simulation modelling. Further research might be undertaken to develop the methods for synthesising all relevant data, both experimental and non-experimental, for use in economic evaluations of public health interventions (Blundell and Dias, 2000).

2) Measuring and valuing outcomes: Long-term outcome (measured in life expectancy or QALYs) is usually required for economic evaluation, so estimating

these health-related outcomes requires extrapolation and valuation. Moreover, some public health interventions affect the health outcome of other individuals who are not being targeted (e.g. co-workers or family members), and the interventions might also involve non-health related outcomes such as educational outcomes; it may be possible to include some of the outcomes within a QALY-type framework but not for others. The issues would be considered as what can be measured versus what should be measured, the need for a more generic measure of wellbeing, sector-specific generic measures of outcome, and greater consideration for alternative evaluation approaches (Lorgelly et al., 2010). Therefore, it would be important to examine which other outcome measurement and valuation methods are valid. The recommendations for measuring and valuing outcomes are that a CBA is based on standard welfare economics and considers all costs and benefits, and the valuation of benefits are based on individuals' willingness-to-pay, which may be limited to ability to pay. Therefore, this approach would consider and value the non-health attributes of a public health intervention such as individuals' ability to return to work or impacts on education and criminal justice systems. In contrast, a CUA is based on a non-welfarist approach, where the benefits of health programmes are measured in terms of health gain (i.e. in QALYs). In addition, the perspective for measuring costs and cost-offsets is covered by the health (and social services) budget on the basis that the objective of the healthcare decision maker is to maximise health gain given the budget constraint. This approach would ignore the impacts of public health interventions on other sectors. Thus, for the broad range of measured costs and outcomes from public health interventions, a cost-consequence analysis (CCA) should be performed following either a CBA or CUA. Moreover, discrete choice experiments (DCE) may provide a useful approach to examining the relative valuation and trade-offs between various attributes including non-health attributes (HM Treasury, 2003, Ryan and Gerard, 2003, Lancsar and Louviere, 2008, Fujiwara and Campbell, 2011). In addition, two methods might be developed as follows: 1) development of sector-specific generic outcomes outside individuals' health (e.g. crime victim QALY, education QALY), and 2) development of a single all-purpose multi-dimensional well-being index or a

uni-dimensional measure of happiness (Dolan et al., 2006). Another alternative approach might be a multi- decision criteria analysis (MCDA), which is a formal approach to make the multiple criteria explicit and to help decision-makers explore different options (Marsh et al., 2014).

3) Identifying intersectoral costs and consequences: The impacts of public health interventions are not only occurred at the individual level, but its effects are also often broad at the community and population levels. As a result, the costs and benefits of those interventions can be associated with many parts of the public sector. Expenditure in some sectors may reduce expenditures in others, e.g. improvements in housing could reduce illness and injuries, with consequent reductions in health care utilisation; the consideration of these issues was limited in the literature reviewed (Weatherly et al., 2009). Therefore, a CCA is suggested to quantify the intersectoral impacts of public health interventions in a way that makes the most sense for each sector. Ideally, each sector would use a well-understood generic measured outcome in reference to whether the shadow price of the budget constraint in the sector could be expressed. Further research to assess an intersectoral compensation test approach was introduced by Claxton et al. (Claxton et al., 2007), and this requires an evaluation of the benefits net of costs which fall on different sectors of the economy; the need for budgetary transfers could then be assessed. Considering broader views, although the public sector is mostly concerned with the impacts of interventions, there should be more consideration of costs on non-profit organisation sector and on private individuals, including the impacts of these costs on the effectiveness of interventions and the need for incentives. In addition, an analyst should consider the costs and consequences by beneficiary group. These groups could be defined in terms of health status, socio-economic status or other characteristics, depending on policy relevance. Finally, research should be conducted to assess whether a general equilibrium approach, which simultaneously considers the consequences of different interventions across all sectors of the economy, is more suitable for the evaluation of public health interventions having a broad range of intersectoral costs and consequences.

4) Incorporating equity considerations: Impacts on equity is important for public health interventions as in many cases, the main objective of the intervention is to tackle health inequalities. Therefore, the distribution of QALYs gained among population subgroups is particularly important in public health. However, there were rarely any mentioned in the studies reviewed (Weatherly et al., 2009). Consequently, primary research should be conducted on the effectiveness of interventions designed to undertake health inequality. It would also be useful to pilot studies to estimate the opportunity cost of a particular equity consideration in terms of population health sacrifice such as the QALYs forgone by pursuing the equitable option compared with the QALY-maximising option. Further research is also required to explore public and stakeholder views on equity weighting in a public health context in order to provide quantitative guidance to policy-makers about how much sacrifice in efficiency (total population health) is merited to pursue particular equity goals. The important issues for this research should also examine socio-economic status, the degree of voluntariness or personal responsibility for health risk, and the value of treatment current illness versus prevention of future health risk.

Furthermore, Edwards et al. conducted a systematic review of the UK and international guidance for the economic evaluation of public health interventions (Edwards et al., 2013). The review described the methodological issues surrounding the economic evaluation of these interventions derived from seven UK guidelines and five international guidelines. The main issue of the methodologies concerns the nature of public health interventions that are complex public health interventions (i.e. involving more than one group or organisation level that is targeted by the intervention). Thus, those guidelines highlighted the methods to deal with a wide range of social and environmental costs and benefits of the interventions, which should ultimately be a broader range of outcomes than focussing solely on QALYs. This is reflected in the common theme of extra-welfarism that underpins the majority of guidance found in the review (Kelly et al., 2003, Weatherly et al., 2009, Payne et al., 2013, HM Treasury, 2003, Byford et al., 2003).

In addition, to capture the equity issues related to the public health interventions, a capability theory was addressed as a means of including equity considerations in the economic analyses of public health interventions (Payne et al., 2013, Lorgelly et al., 2010), since the capability theory considers the distribution of capability across society. Although the argument that further research should focus beyond QALYs is introduced, it should also consider usefulness of measured QALYs. Decision-making could be difficult without the information to inform whether public health interventions are cost-effective compared to the cost-effectiveness threshold (National Institute for Health and Care Excellence (NICE), 2012). In conclusion, a 12-point checklist for considering the methodological guidance of economic evaluation of public health interventions was proposed to highlight the additional key challenges related to public health interventions. Further research needs to address these issues in the study design and reporting of economic evaluations of public health interventions as shown in Table 1-4 (Edwards et al., 2013).

Table 1-3 Checklist of considerations when considering published guidance for the economic evaluation of public health interventions

1	What is the appropriate theoretical framework for analysis, e.g. welfarist, extra-welfarist, capability theory?
2	What is the setting of the public health intervention under evaluation? (e.g. environmental change; infectious disease control; screening; supporting behaviour change; supporting government legislation or policy)
3	Is this best described as a primary, secondary or tertiary prevention intervention, i.e. upstream or downstream?
4	What is the main agency (government; health service; local government; voluntary sector) responsible for implementation and who are the key stakeholders?
5	If this is an intervention aimed at behaviour change, what are the key levels of change (legislation; price; changing social norms; choice architecture and nudging)?
6	What is the appropriate time horizon of analysis and what is the most appropriate discount rate for costs and outcomes?
7	If the public health intervention aims to "shift the curve", are we most interested in the centre or tails of the distribution?
8	How is this public health intervention likely to impact inequalities in health?
9	Will subgroup analysis help identify the range of cost-effectiveness estimates across different settings, delivery methods and population groups?
10	What are the main outcome measures of interest, e.g. QALYs/DALYs or a large range of outcome measures relating to health and wider social outcomes?
11	How important is it to value costs, benefits and returns in monetary terms? Is it reasonable to expect the intervention to be cost saving in the short, medium or long term?
12	How relevant will it be to compare an ICER with the NICE threshold of £20,000-30,000 or an international equivalent?

Source: (Edwards et al., 2013)

1.8 Modelling approach for economic evaluation of public health interventions

Public health policy-makers have been faced with decision problems of how best to allocate scarce resources in order to maximise value for money. Modelling is frequently being applied as a method of depicting the complexity of decision making with respect to interventions and to more accurately capture the associated costs and benefits in economic evaluations. A modelling approach for an economic evaluation of a public health intervention has been increasingly applied for policy analysis to support the design of efficient and effective policy options for complex public health problems (Ashley et al., 2015,

Atkinson et al., 2015, Brennan et al., 2014a, Brennan et al., 2014b, Cadilhac et al., 2011, Chisholm et al., 2004, Galea et al., 2009). The approach would allow simulated experimentation of policy scenarios to test their comparative impact and cost over the short, medium, and longer term (Atkinson et al., 2015). The policy analysis tool could test the effectiveness and cost-effectiveness, equity of policy responses, exposing unintended consequences and perverse incentives in the system through computer simulation, and averting the need for costly trial and error approaches. This alternative approach should be considered to support decision-making for future strategies to address complex problems.

1.8.1 Classification of model structure for economic evaluation

There are several existing classification systems for health economic models. This chapter applied the model classification adapted from Brennan et al. (2006). The classification was based on whether a model is cohort- or individual-based, discrete or continuous time-dependent, and whether it allows for interactions between individuals, for example, infectious diseases – which are transmitted from person to person by direct or indirect contact (Brennan et al., 2006). The range of available modelling approaches for model-based economic evaluations are shown in Table 1-5.

Table 1-4 Classification of model structures

	Cohort/Aggregate level	**Individual level**
No interaction allowed	Decision tree/Markov model	Individual sampling model (ISM)/Individual-based microsimulation
Interaction allowed	System dynamics model/Markov chain model	Agent-based model/Discrete event simulation

Adapted from (Brennan et al., 2006)

The most common types of model that do not involve interaction are decision trees and Markov models for the cohort or aggregate level, which allocate individuals to compartments that are homogeneous (Barton et al., 2004). The decision tree is the simplest structure where all plausible patient pathways are shown on decision trees together with associated probabilities and outcome measures. The decision tree model is generally used for the short time horizon. However, there is a limit to manageable size of a probability tree such as recurrence event and survival time after treatment. To avoid an infinite number of branches in the decision tree, it is necessary to consider survival times, and the tree can be simply drawn as a Markov model.

Markov models are commonly used in economic evaluations. The main benefit is the easy representation of recurrent events with a fixed time cycle but they do not allow for interaction between individuals. For the individual level without interaction, an individual sampling model and individual-based microsimulation have potentially heterogeneous characteristics that affect their progression through the model (Barton et al., 2004, Brennan et al., 2006). Its key advantage lies in modelling multiple co-morbidities which depends on multiple attributes or covariates. Individual-based models can simulate complex patterns of disease evolution to emerge and allow for more realistic scenarios. For example, an individual-based microsimulation can simulate the

life-time trajectories of participants and record participants' histories. The transitions across different states may be conditional upon previous events/history that participants have gone through.

In contrast, interaction between individuals needs to be taken into account in two main circumstances: when modelling infectious diseases - where the risk of an individual catching the disease depends on how many other people already have it; and when constraints on resources means that the choice of treatment for one patient affects what can be given to another (Barton et al., 2004, Brennan et al., 2006). Where interaction is an important issue in modelling and individual characteristics may be heterogeneous, two methods are suggested: 1) an agent-based model allows agents (people who have certain heterogeneous features) to act autonomously within their own behaviour rules and to interact with each other and their environment (Chhatwal and He, 2015); and 2) a discrete event simulation model can be used for modelling disease progression as a continuous process with time-varying event rates and prior events affecting subsequent event rates.

For the aggregate level, system dynamics are required. System dynamics is a simulation modelling method used for representing the structure of complex systems and understanding their behaviour over time (Marshall et al., 2015). The model provides a cross-sectional view of a system by counting the number of people exhibiting particular combinations of characteristics or in specific transitional health states over time. System dynamics and agent-based modelling can be used to develop a tool for policy analysis (Atkinson et al., 2015). The models take into account the interrelations, reciprocity, discontinuity, and dynamic nature of influences on health and health behaviours within a broader context (Marshall et al., 2015). They allow for virtual experimentation of policy scenarios to test their comparative impacts and costs over the short, medium, and longer term. The policy analysis tool could test the efficiency, effectiveness, and equity of policy responses, exposing unintended consequences and perverse incentives in the system through computer simulation and averting the need for costly trial and error approaches (Hoang et al., 2016).

1.8.2 Incidence-based versus prevalence-based economic evaluation

There are two main approaches for conducting economic evaluation that have been used to provide important information when a new healthcare intervention is introduced to a target population (Mauskopf, 1998):

1) A*n incidence-based* economic evaluation follows a disease cohort for the duration of the disease and estimates discounted and health gains with alternative interventions. The cost-effectiveness ratio is based on individual utility maximization and provides information to decision-makers about the efficiency of a new intervention compared to societal willingness-to-pay for health gains. It does not estimate annual budget impacts, and generally does not capture indirect effects on the population.

2) *A prevalence-based* approach provides estimates of costs and health benefits for the total population for either 1 year or over a longer time horizon on a cumulative basis. Appropriate threshold values for these ratios are those based on a percentage of Gross Domestic Product (GDP) as recommended by the WHO (Single et al., 2003). The prevalence-based cost-effectiveness ratio provides information to decision-makers on the affordability of the new intervention and the value for money over the selected time horizon. The prevalence-based analysis can take into account both direct and indirect effects of healthcare interventions, and is therefore frequently used for economic evaluations of vaccine programmes (Capri et al., 2011, Kawabayashi et al., 2013) as well as cost-of-illness studies such as social cost estimates of substance abuse (John et al., 2009, Xie et al., 1998, Saar, 2009, Jarl et al., 2008).

Table 1-6 compares the key features of the two method (Mauskopf, 2012). The prevalence-based approach is more suitable for ascertaining the total current economic burden of a disease (WHO, 2009, Rehm et al., 2009, Collins et al., 2006), whereas an incidence-based approach is more useful for ascertaining the expected impact of a disease in the future (and its potential

prevention or elimination). For ongoing health and social problems such as illicit drug use, the results of prevalence-based and incidence-based estimates are often similar (WHO, 2009). For health problems that are declining in magnitude (such as smoking in some countries), prevalence-based estimates will generally be higher than incidence-based estimates. For emerging health issues such as HIV or hepatitis infection epidemics, incidence-based estimates generally provide higher estimates than prevalence-based estimates because many infected persons may still be in the latency phase of the diseases.

Prevalence-based economic evaluations might be of greater use for healthcare and public health policy-makers than incidence-based methods because it estimates value for money and provides estimates of budget impact as well as population health impact (both direct and indirect effects) (Mauskopf, 1998, Mauskopf, 2012). However, the economic evaluation results derived from the prevalence-based approach are not comparable for the cost-effectiveness threshold. Many cost-effectiveness studies using incidence-based method could produce incremental cost-effectiveness ratio compared with the threshold to determine whether the new intervention for the specific health problem is a good value for the money (Drummond MF et al., 2005). This type of value measure is also very useful if decision-makers are trying to determine the best way to allocate healthcare budget between alternative uses; that is, they should allocate the budget to the new intervention with the lowest cost-effectiveness ratios first. In conclusion, conducting both prevalence-based and incidence-based analyses can give a complete picture of the efficiency and affordability of a new intervention, and provide a useful tool for policy-makers to determine optimal resource allocation and good value for money. Thus, both approaches should be conducted for all types of healthcare interventions (Mauskopf et al., 2007).

Table 1-5 A comparative analysis of incidence-based and prevalence-based methods for economic evaluations

MODEL CHARACTERISTIC	INCIDENCE-BASED ECONOMIC EVALUATION	PREVALENCE-BASED ECONOMIC EVALUATION
Basis in economics theory	Utility maximisation	None
Threshold value	Societal willingness-to-pay per QALY gained	Affordability thresholds, e.g. relative to GDP
Population	Single cohort, can represent different population subgroups	Total population or population subgroups
Time horizon	Duration of treatment impact on the single cohort	After approval for use, annual values or cumulative value for a specified number of years or to steady state
Treatment comparators	Current practice compared with a new intervention	Current mix of interventions compared with a predicted mix of interventions, including the new intervention
Market shares	100% with each comparator	Current intervention mix based on observed market shares; new mix with new intervention available based on predicted market shares
Indirect health effects	Generally not considered	Generally considered
Catch-up effects when first approved	Not considered	May or may not be considered
Uptake/coverage	Uptake/coverage has no effect on the results because only direct effects are considered	If indirect effects are included, uptake/coverage impacts the results
Outcomes	Cumulative costs for single cohort for chosen time horizon; cumulative effectiveness measured in natural units or QALYs for chosen time horizon; ratio of costs to effectiveness; results do not vary with market share; results may vary for population subgroups	Annual or cumulative population costs; annual or cumulative population effectiveness measured in natural units or QALYs; ratio of costs to effectiveness; results will vary with market share and for population subgroups
Value to decision-maker	Estimates the efficiency of a therapy compared with a standard of care for target cohorts, and incremental cost-effectiveness ratio	Estimates population budget impact over time for budget planning, health outcomes over time for the population, and ratio of costs to health outcomes

Source: (Mauskopf, 2012)

1.8.3 Time lag of alcohol consumption changes and alcohol-related harm changes

In recent literature, studies are using time series analyses to show the association between per capita alcohol and changes in rates of alcohol-related harms over a period of time (Bye, 2007, Engdahl and Ramstedt, 2011, Jiang et al., 2015, Ramstedt, 2001, Ramstedt, 2008). However, alcohol use, particularly heavy episodic drinking, is associated with several short-term negative consequences (such as injuries and violence) as well as long-term effects, including greater risk of alcohol dependency and other chronic diseases (Grant et al., 2009, Jones and Bellis, 2014, Jones et al., 2008, Kendler et al., 2016, Rehm and Roerecke, 2013, Roerecke and Rehm, 2013). An important methodological issue has been raised as the time lag between alcohol consumption and its related harm changes i.e. the time to first effect, the duration to full effect, and the functional form of the accumulation of effect (Holmes et al., 2012).

A recent review summarised the derived time lag specifications when modelling the effects of aggregate alcohol consumption on the rates of various alcohol-related harms (Holmes et al., 2012). It showed limited consistency across studies as well as a limited number of the alcohol-related conditions which were under evaluated. The lag structures used typically specified the immediate effect as the greatest single year effect, with effects of declining magnitude seen in subsequent years. The size of the first-year effect showed approximately 20-60% of the total effect but the reason for the different effect was unclear. The variation of lag time for the full effect of changes in aggregate alcohol consumption was found to be five years and over. Based on the best available evidence, an aggregate-level alcohol policy model applied no lag time for the effect of alcohol consumption change on acute alcohol-related harms; however, for such effect on chronic alcohol-related conditions, the alcohol policy model specified an immediate effect with linear functional form and ten years to full effect (Brennan et al., 2014a, Brennan et al., 2014b). Holmes et.al. (2012) suggested the further work that might investigate aetiology of alcohol-related harms at individual-level with awareness given to

the relevance of initial volume and patterns of consumption; moreover, other issues might be considered, i.e. exposure period for disease development, evidence of protective effects, influence of competing risks, risks for different social groups and the functional form of those risks (Holmes et al., 2012). At the population-level, one challenge is to address whether lag response differs for consumption increases and decreases and the examination of age, period, and cohort trends - which may also distort temporal processes. Future research attention needs to be given to the rationale for choosing or applying particular lag specifications and the inherent complexity of the processes which aggregate to create time lag effects.

1.8.4 Review methods for modelling cost-effectiveness in public health intervention

To conduct a modelling cost-effectiveness study of a public health intervention, the methodological problems include (Marsh et al., 2012): 1) difficulty in estimating for how behaviours change over time for a modifying risk behaviour intervention, e.g. whether a short-term improvement in diet is likely to be maintained (Alayli-Goebbels et al., 2014); 2) how the long-term health impacts of behaviours is estimated and the time lag between behaviour changed and incidence of disease when a risk behaviour is modified, e.g. the impact of sedentariness on the incidence of heart disease (Alayli-Goebbels et al., 2014, Holmes et al., 2012); 3) what the impacts are of population interactions for a population-level intervention, e.g. sexual behaviour and herd immunity (Marshall et al., 2015, Martineau et al., 2013); and 4) for heterogeneity among individuals, how their multiple co-morbidities or risk behaviours are taken into account such as conditions associated with alcohol use disorder (Caro et al., 2010, Chhatwal and He, 2015). Moreover, many literature identified these fundamental features of modelling approaches that can be used to guide the implementation public health economic evaluation modelling (Brennan et al., 2016, Briggs et al., 2016, Marsh et al., 2012, Martineau et al., 2013, Alayli-Goebbels et al., 2014).

For behavioural interventions, models can be built where simulations take place at a cohort or aggregate level, or to allow the behaviour of individuals to be tracked separately. Cohort-level models - such as cohort Markov models often employed by health economists - allocate individuals to compartments, and require that individuals within a compartment or cohort are homogeneous (Barton et al., 2004, Brennan et al., 2006). Such cohort models are easier and less resource-intensive to construct than individual-level models but there are limitations when the models are applied for public health interventions. First, the homogeneity assumption is often not satisfied, e.g. if future model states depend on an individual's history. For example, the health impact of an individual quitting smoking will depend on the individual's historical consumption of tobacco and alcohol. Second, cohort models become very complex if they need to capture multiple co-morbidities such as those associated with alcohol use disorder - which has been linked with multiple health problems.

In response to these challenges with cohort-level models, a number of individual-level modelling techniques have been proposed including individual-level Markov models, Discrete Event Simulations, and agent-based models (Caro et al., 2010). Of particular interest to public health economic evaluations is agent-based models, which allows agents to act autonomously with their own behavioural rules. Many public health interventions are designed to influence peoples' behaviour such as improving physical activity levels or causing people to quit smoking. The economic evaluation of such interventions will require an understanding of how peoples' behaviours respond to these interventions, and how these behavioural impacts are maintained, or otherwise, over time. Agent-based models have an important role to play in such assessments (Alayli-Goebbels et al., 2014). Therefore, the selection and implementation of appropriate modelling approaches will be supported by the development of a better empirical understanding of behavioural dynamics and the relationship of behaviour and health (Marsh et al., 2012). For instance, existing panel survey data should be analysed to determine the dynamics of relevant public health behaviours such as physical activity, diet, smoking, alcohol consumption, and

sexual behaviour. This evidence should also be analysed to determine the impact of these behaviours on health outcomes by age and accumulated behaviour.

1.9 Transferability of economic evaluations across jurisdictions: methodological challenges and recommendations

An increasing number of national decision-making processes have requested economic evaluations for developing reimbursement packages of pharmaceuticals and other health interventions. Since there are many factors that would affect the cost-effectiveness of health technologies under evaluations between jurisdictions (Sculpher et al., 2004), most of the national HTA guidelines recommend to conduct the economic evaluation relevant to the local context; moreover, decision-makers also prefer cost-effectiveness studies that are applicable in their own setting. However, a full economic evaluation using local data requires substantial resources both in terms of finance and time consumed as well as technical health economics expertise. These are challenging problems faced by those involved in the decision-making process, especially for low- and middle-income countries (Drummond et al., 2015).

Therefore, decision-makers might need to use analyses or data from other countries and consider whether the results are generalisable or transferable. Studies are considered generalisable when they are able to be applied to a range of jurisdictions without any adjustment needed for interpretation (Barbieri et al., 2010, Drummond et al., 2009). Moreover, some studies are transferable if they can be adapted to apply to other settings. Finally, some of them are so specific to a given jurisdiction that they are simply not transferable to other jurisdictions.

1.9.1 Summary of HTA guidelines related to transferability of economic evaluation

There are a number of reviews of existing national HTA guidelines (Barbieri et al., 2010, Drummond et al., 2015, Drummond et al., 2009, Goeree et al., 2007, Goeree et al., 2011). These reviews assessed the wide range of the HTA guidelines related to the transferability of economic evaluations and HTA across jurisdictions (also referred to as geographic transferability). Barbieri et al. summarised and classified the level of transferability of key data input used in economic evaluation from 37 guidelines, i.e. baseline risk, treatment effect, health state preference values (utilities), resource used, and unit costs (prices) as shown in Figure 1-6 (Barbieri et al., 2010). For baseline risk and treatment effect, no details were given in 4 cases while they were discussed in 12 cases. For health utilities, no information was given in 16 cases. Resource use and unit costs were discussed together in 5 cases while no details were given in 2 cases for unit costs and in 6 cases for resource use.

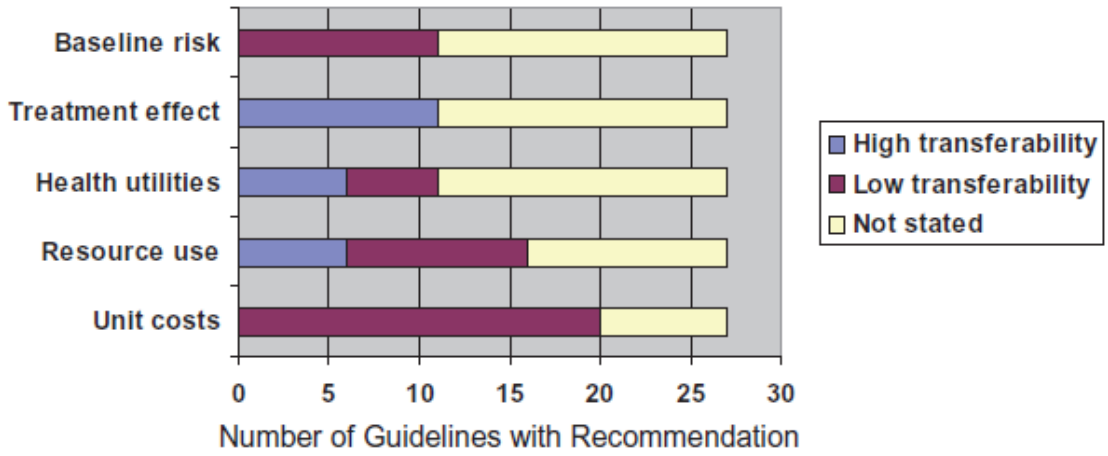


Figure 1-5 Level of transferability of data inputs (as summarised from 37 national HTA guidelines)

Note: "High transferability": elements of economic evaluation from other locations can be used in local analyses; "Low transferability": data from other jurisdictions are not accepted or there is a strong preference for local data; and "Not stated": no details were given or the item of interest was not discussed separately from another item.

Source: (Barbieri et al., 2010)

There was great variation in detail and significance given to the issue of the transferability of data. It appeared that there was a general agreement among guidelines on which data were more or less likely to be transferable between jurisdictions (Barbieri et al., 2010). The review provides the full list of 37 national HTA guidelines including the most recent year of updated version at http://www.ispor.org/publications/value/vihsupplementary/vih13i8_drummond.asp.

1) *Clinical data baseline risk and relative treatment effect:* In all cases where baseline risk and treatment effect were discussed separately, baseline risk was considered to have low transferability while treatment effect was generally considered to have high transferability. Even in cases of high transferability, the guidelines suggested giving attention to the applicability of trials to the local context (e.g. differences between trial patients and local population, and adequacy of comparators). The main reason for using country-specific data for baseline measures of clinical events was the potential difference in epidemiological data between locations where the use of estimates from other settings could be misleading. In contrast, treatment effect (e.g. relative risk of an intervention with respect to a comparator) was transferable between locations. In this case, the use of high quality data (e.g. from systematic reviews or large RCTs) was recognised as a key factor and more important than the use of local data. Therefore, one recommendation was to obtain treatment effects from multinational RCTs and then adjust the estimates of baseline risk derived from local population-based sources. Nevertheless, in some cases, the guidelines highlighted the need for potential adjustment of the results obtained from a clinical trial to the local context, given the potential differences between settings (mainly in terms of population characteristics). Those guidelines generally suggested that clinical data are transferable, but with adaption to account for differences in some factors. Among these factors, epidemiological data, patient characteristics, comparators used, and clinical practice are often considered.

2) *Health state preference values (health state utilities):* A variation of recommendations were made about the transferability between locations of utility estimates; these differences were mainly caused by different degrees of flexibility in the various national HTA guidelines for accepting data from other locations based on the availability of these data in the country. In many cases, health state preference values are not available for the country of interest such as countries where the use of economic evaluations might be less developed so it is often recognised that utilities need to be obtained from other countries. In these cases, great attention is given to the need for transparency, in that the data sources and instruments used should be stated together with a discussion of their applicability to the country of interest. Finally, sensitivity analyses are often recommended when utility values are obtained from studies performed in other settings.

3) *Resource use and unit costs:* The majority of the guidelines recommended obtaining resource use from the local setting, since the variation of clinical practices, incentives and regulations, health financing, healthcare systems and schemes, and distribution of resources were often mentioned as the reasons of different resource use between locations. These guidelines suggest that it is fundamental to use local data for resource consumption and estimates obtained from other locations are often not considered as an appropriate and valid source. In general, these guidelines stated that if resource utilisation estimates are obtained from published studies performed in other locations, they should be adapted to the country of interest, e.g. by means of expert opinion. Also, they suggested that any method used to adjust resource use from other locations to the country of interest should be explained and justified. Regarding unit costs, most guidelines that analysed these data separately from resource use agreed that they must be jurisdiction-specific because of differences in relative and absolute prices between countries. Some guidelines also provided sources for unit costs in form of an official list. Most guidelines recommend presenting quantities of resource use separately from unit costs to increase the transparency of the analysis.

1.9.2 Methods recommended for addressing issues of transferability

There are two methods to deal with the issue of transferability of data classified by types of economic evaluation (Barbieri et al., 2010):

1) Economic evaluations based on individual patient data: Most guidelines did not make any recommendations on methods for transferring data from clinical trials carried out in other countries or multinational trials (with or without the inclusion of the reference countries). Some guidelines recommended that clinical data from trials performed in other settings were acceptable based on in particular of the relative treatment effect, while absolute risk estimates or resource consumption from these studies were difficult to transfer to other settings. Those guidelines also suggested that clinical data from multinational trials could be pooled - although this may not be the case for all interventions - while economic data are unable to be pooled because of the potential differences in resource use and clinical practice patterns between centres and countries.

The NICE guidelines in England and Wales state that statistical pooling of clinical data should be accompanied by an assessment of clinical heterogeneity. Emphasis is also given in the Australian guidelines to the need for assessing the heterogeneity of patients by means of subgroup analysis or meta-regression, while the Canadian guidelines are the only ones that recommended the use of multilevel models (in addition to other methods such as multivariate regression models) to address the issue of clinical and economic differences between centres and countries in a multinational study.

2) Economic evaluations based on decision models: The use of a decision model is often viewed by the guidelines as a method to handle the variability and differences among settings. For example, both the Dutch and Swedish guidelines explicitly stated that modelling is the key method for transferring data obtained from other countries to the local context. Other guidelines also said that the use of modelling should help to address the issue of transferability

among jurisdictions (mainly by means of sensitivity analyses). The need for adapting the model structure to the local context is explicitly mentioned only in the Belgian and Spanish guidelines where it is stated that adjustments to models may be needed, especially when there are differences in practice patterns.

Nevertheless, most of the guidelines state that an external validation of the model should be conducted to confirm that the model structure adequately reflects the clinical patterns and underlying nature of the disease in the local context. Study selection and methods to synthesise data are considered important issues for appropriately populating decision models. In general, it seems that the guidelines gave more importance to the quality of the studies used as the source of effectiveness data rather than to their specific setting. RCTs are generally preferred as the source of clinical data even when they were the reference country; however, it is often stated that clinical estimates need to be appropriate for the study question and target population. In addition, some of the most detailed guidelines (Canada, United States, England, and Wales) stated that the preferred method for incorporating estimates of treatment effectiveness was to combine relative risk estimates from international RCTs with estimates of baseline risk from local epidemiological data. When data from more than one trial are available, meta-analysis is the preferred method for synthesising clinical data. Some guidelines (Australia, England, and Wales) stated that it was important to take account of the heterogeneity among studies included in the meta-analysis, e.g. by means of random-effect models or meta-regressions.

The NICE guidelines also suggested that some studies included in the meta-analysis could be excluded in a sensitivity analysis to assess the impact of different sources of data on cost-effectiveness results. The need for local sources of economic data to include in the decision model is highlighted by most of the guidelines, often recommending the use of expert opinion when no valid published data are available. Finally, most guidelines stated that the issue of transferability between countries should be addressed by means of sensitivity analyses.

Chapter 2: Review methods for modelling economic evaluation of an alcohol intervention

2.1 Introduction

As mentioned in Chapter 1, there are methodological issues surrounding model-based economic evaluation of public health interventions, e.g. comprehensive evidence for effectiveness which incorporate programme complexity, time lag between behaviour changes and its related harm changes, use of incidence-based versus prevalence-based approaches, and measurement and valuation of health outcomes and wider benefits. This chapter reviews the previous model-based economic evaluation studies of alcohol interventions. The next section presents the methods used for the systematic search where the selection criteria and search strategy are reported. This is followed by the methods used for the methodology extraction of the selected studies. The following two sections report the results of the systematic search and the results of the methodology extraction. The limitations of the methodological review are then considered. The last section presents a critique of the method used in the studies reviewed. This methodological review is used to inform the development of an economic model for alcohol intervention in the following chapters.

2.2 Research questions

The research questions are:

1. What are the current evidence of modelling economic evaluations of alcohol interventions?
2. What are the methodological challenges of economic evaluations of alcohol interventions to inform public health policy about value for money?

2.3 Objectives of the review

This literature review aims to examine and compare the modelling methods used in published economic evaluations of alcohol interventions, i.e. types of economic evaluations, types of models, approaches for measurement and valuation of the consequences, identification of the individual-level and population-level consequences, and other economic evaluation components (e.g. perspective and time horizon). Moreover, the review aims to define the evidence gap of developing alcohol policy and intervention modelling so the current study can likely be used to fulfil the gap.

2.4 Methods

Only full economic evaluations – which capture both relevant costs and benefits – were considered in this review (Drummond MF et al., 2005). The following two sections present the methods for the systematic search, the selection criteria, the assessing quality of eligible studies, and the data extraction.

2.4.1 Systematic search

Studies of model-based economic evaluations of alcohol interventions were identified by searching the following sources:

1) Electronic databases - NHS Economic Evaluation Database (EED), which identifies potential economic evaluations by searching the following databases: MEDLINE (from 1995 to the end of December 2014), EMBASE (from 2002 to the end of December 2014), PsychINFO (from 2006 to the end of December 2014) and CINAHL (from 1995 to the end of December 2014). Afterward, the search of additional studies from MEDLINE and EMBASE was conducted starting from December 2014 to December 2016.

2) Reference lists and citation tracking - bibliographic search for reference lists of retrieved studies and citation tracking of key papers using MEDLINE and EMBASE.

The search terms are presented in Appendix 2. Searches of electronic databases used free-text terms and MESH headings. The search terms were conducted using keywords included type of intervention, study design, and type of costs/ consequences. The search terms were: (alcohol-related disorders or alcohol dependence or heavy drinking or alcohol misuse) and (economic evaluation or value for money) and (health promotion or behaviour therapy or harm reduction or treatment or brief intervention). The retrieved citations were managed using Endnote X7.

2.4.2 Selection criteria

The selection criteria (Table 2-1) were applied to screened and selected eligible studies. Both inclusion and exclusion criteria are defined in terms of type of study, type of modelling approach, types of participants, types of interventions, and types of costs and consequences. Decisions about the inclusion or exclusion of studies are made according to these criteria.

2.4.3 Assessing quality of eligible studies

No specific quality assessment tools were developed to assess the quality of economic modelling studies of public health interventions. As mentioned in Chapter 1, there were key methodological challenges surrounding economic evaluations of public health interventions. Thus, this review applied the recommendations of two systematic reviews of economic modelling studies. The first review was conducted by (Philips et al., 2004) that developed the quality assessment tool of decision-analytic models. In addition, the second review summarised the key challenges for developing the structure of public health economic models (Squires et al., 2016). In conclusion, the main issues for assessing quality of eligible studies were as follows: model structure, data identification, data modelling, assessment of uncertainty, inclusion of non-healthcare costs and outcomes, inclusion of equity, and internal- and external-consistency.

2.4.4 Data extraction

Study participants and level of implementation (i.e. individual, community, and population levels) were extracted. Moreover, the alternative alcohol interventions – which were in specific settings or national level - of each study are described. Studies were classified as the full economic evaluation type, i.e. cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA). The different study types affected how the costs and outcomes were identified, measured, and valued. The modelling approaches were defined based on classification of the model structure in Chapter 1 as well as other components such as time horizon and perspective on cost and benefits (e.g. patients' perspective, healthcare sector perspective, and societal perspective). Moreover, a level of consequences considered whether alcohol-related harms affected others including alcohol-related victims and drinkers' families – which arose from individual's drinking problems.

Table 2-1 Inclusion and exclusion criteria

	Inclusion criteria	**Exclusion criteria**
Types of studies	Only full economic evaluations are included. Included studies are classified as CEA, CUA, and CBA and incorporated a modelling approach (as shown in Table 2-1).	Partial economic evaluations are not included. Partial economic evaluations include studies such as cost-offset analysis, cost-outcome description, cost description, efficacy or effectiveness evaluations, and outcome descriptions. Also excluded are systematic reviews and methodological studies.
Types of participants	Study population is the target of an alcohol intervention at both individual and population levels.	The population of interest is not the target of a specific alcohol intervention. Foetal alcohol spectrum disorder patients are also excluded.
Types of interventions	Included interventions are alcohol interventions that aim to reduce alcohol consumption, i.e. screening followed by counselling problem drinker, alcohol use disorder treatment, and interventions delivered at a population level such as: 1) alcohol policy and legislative interventions (alcohol taxes, drink driving controls, licensing provisions, and alcohol advertising policy); 2) enforcement measures of legislation; and 3) prevention of alcohol misuse (school-based interventions and mass media campaigns).	Studies that evaluate treatment for alcohol-related disease and do not aim to reduce consumption are excluded. Mixed interventions of modified risk behaviours and alcohol mixed with other substance use disorders are not included due to the difficulty of separating identification, measurement and evaluation procedures for the different treatments or target population. Screening and detection studies (screening instruments for the detection of problem drinking, alcohol abuse and dependence and the laboratory tests that confirm results or monitor abstinence) are excluded.
Types of costs and consequences	Economic evaluations that allow an assessment of the identification, measurement and valuation of outcomes, and cost domains are included.	Studies that are a methodological extension of another one are excluded and only the published study with a more complete description of the methodology applied is selected.

2.5 Results

As presented in Figure 2-1, the initial search of databases yielded 1,370 articles, and 1,338 duplicates and non-relevant studies were removed by screening titles and abstracts. The full articles of 37 studies were reviewed to assess eligibility based on inclusion criteria. Subsequently, 26 studies were eligible for further methodological review, and the following number of studies were conducted in these respective countries: the US (n = 5), Australia (n = 5), the UK (n = 4), the Netherlands (n = 2), Denmark (n = 2), Italy (n = 1), Sweden (n = 1), Thailand (n = 1), Estonia (n = 1), East Africa (n = 1), Germany (n = 1), Canada (n = 1), and 12 WHO sub-regions (n = 1). Table 2-2 and Table 2-3 present the approach used for model-based economic evaluations of alcohol interventions.

2.5.1 Interventions

The majority of interventions were targeted at specific at-risk drinkers and in healthcare settings (n = 17), e.g. primary care, emergency department, and outpatient department. Ten studies assessed population-level interventions, and a study evaluated an intervention at the community-level setting (the number of study settings was greater than the total number of eligible studies due to some studies evaluating multiple settings). The most commonly modelling studies evaluated the cost-effectiveness of screening and brief intervention (SBI) for alcohol use disorder, where the efficacy of the intervention was also reported in terms of reducing alcohol drinking problems (Angus et al., 2014a, Barbosa et al., 2015, Barbosa et al., 2010b, Gentilello et al., 2005, Kapoor et al., 2009, Kessler et al., 2015, Mortimer and Segal, 2005, Neighbors et al., 2010, Purshouse et al., 2013, Quanbeck et al., 2010, Zur and Zaric, 2016, Smit et al., 2011). Those studies examined the relationships between SBI and changes of consumption and/or alcohol-related harms within the follow-up period; moreover, the changes of consumption level were modelled to estimate the changes of alcohol-related diseases and/or other harms over time. Furthermore, the studies conducted economic evaluations

alongside RCTs with a short-term follow-up period and used the modelling approach to extrapolate the costs and outcomes beyond the end of clinical trial (Barbosa et al., 2015, Barbosa et al., 2010b, Braithwaite et al., 2014, Brodtkorb et al., 2016, Laramee et al., 2014, Navarro et al., 2011, Navarro et al., 2014, Palmer et al., 2000, Purshouse et al., 2013, Tariq et al., 2009). In addition, the mathematical modelling evaluated the cost-effectiveness of population-level interventions such as pricing and taxation policies, drink-driving policies, advertising bans, and licensing controls (Byrnes et al., 2010, Chisholm et al., 2004, Cobiac et al., 2009, Holm et al., 2014b, Holm et al., 2014a, Ditsuwan et al., 2013, Bye, 2007).

2.5.2 Types of economic evaluation and modelling approaches

Most of these modelling studies used CUAs (n = 19) as the analytical method, followed by CEAs (n = 6), and only two studies used CBAs. In terms of the type of model used, decision trees (6 studies) and cohort-based Markov models or multistate cohort population models (16 studies) were commonly used, followed by system dynamics model (2 studies) where both studies evaluated interventions for people living with HIV/AIDS and the effect of HIV-related morbidity and mortality - and individual based microsimulation model (2 studies); there was no agent-based model/discrete event simulation model. The time horizon used for a majority of the modelling studies was more than 30 years (n = 14), followed by less than 10 years (n = 8) and >10-30 years (n = 4). The long-term evaluations allowed the model to capture the benefits of the public health interventions. Input parameters for conducting model-based economic evaluations were gathered from multiple sources of epidemiological studies as well as meta-analyses of previous trials to estimate future costs and outcomes.

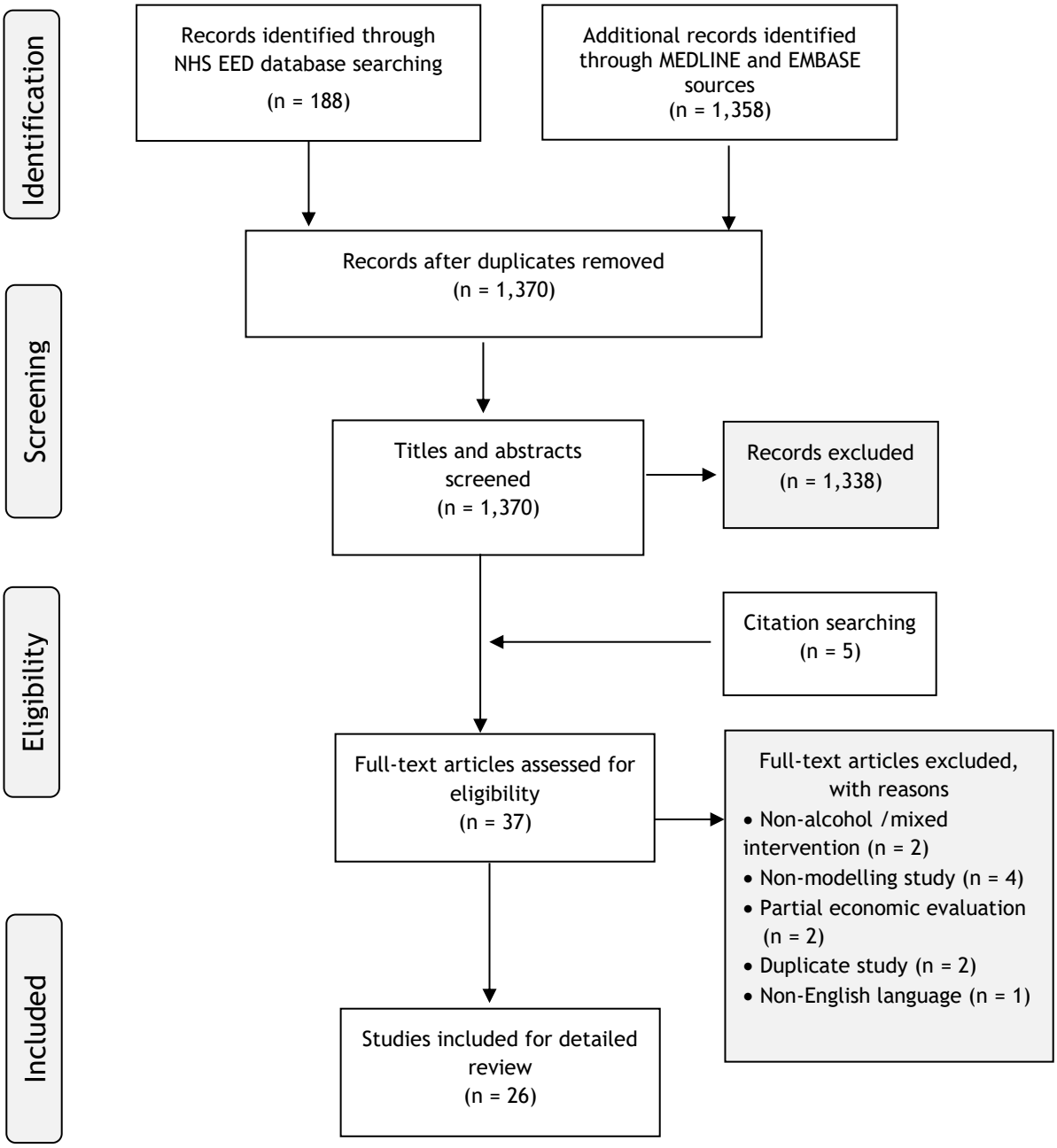


Figure 2-1 Flow chart of literature search

Table 2-2 Summary of eligible studies

Models used	Decision tree	Cohort Markov[a]	System dynamics	individual based microsimulation model	Total
	n=6	n=16	n=2	n=2	n=26
Type of economic evaluation[b]					
CEA	3	2	1	-	6
CUA	4	13	1	1	19
CBA	-	1	-	1	2
Level of implemented intervention					
Individual	5	10	-	2	17
Community	1	-	-	-	1
Population	2	6	2	-	10
Level of consequences					
Individual	4	15	-	1	20
Others	-	-	-	1	1
Individual and others	2	1	2	-	5
Perspective[c]					
Employer	-	-	-	2	2
Healthcare sector	7	12	2	-	21
Societal	1	4	-	-	5
Time horizon					
0.5-10 years	3	4	-	1	8
>10-30 years	-	2	2	-	4
>30 years	3	10	-	1	14

[a] Includes a decision tree combined with Markov model

[b] One study used both a CEA and CUA.

[c] Two studies used both healthcare sector and societal perspectives.

Table 2-3 Characteristic of 26 eligible economic modelling studies

Author, year	Country	Study participants	Implementation levels	Intervention	Study type	Modelling approach: time horizon	level of consequence	Perspective	Summary of quality assessment
(Angus et al., 2014b)	Italy	The screening of patients when they next registered with a new GP and screening when they have their next standard GP consultation (subgroup by age, sex and mean alcohol consumption at baseline)	Individual level	10 years SBI programmes in primary health care in Italy (screening annually and not more than once) screening is modelled using the AUDIT-C questionnaire with a threshold of 4 for women and 5 for men with a brief intervention lasting 10 minutes for all patients who screen positive	CUA	Aggregate model /Sheffield Alcohol Policy Model (SAPM): 30 years	Individual	Italian National Health Service (INHS)	The SAPM developed in the UK was employed using an Italian baseline data on consumption, morbidity, mortality, and cost. Model structure was that the intervention affected consumption. Then, morbidity and mortality risks related to consumption were derived from SAPM. Harms to others were not included, and only health outcome was measured (i.e. QALYs). Sensitivity analyses were conducted by varied discount rate, model assumptions, and implementation options
(Barbosa et al., 2015)	The US	Patients in Emergency Department and OPD	Individual level	Delivering alcohol screening, brief intervention, and referral to treatment (SBIRT) in emergency departments (ED) when compared to outpatient medical settings	CUA	Decision tree: 6 months	Individual and others (criminal activity, accident, and income loss)	Provider and societal	A probabilistic decision analytic tree categorized patients into three health states based on drinking level. Data were observational and administrative, supplemented by survey data and the literature. Social costs were also estimated. Health outcome was measured (i.e. QALYs). Probabilistic sensitivity analyses were conducted.
(Barbosa et al., 2010b)	The UK	Males who are seeking alcohol treatment	Individual level	Based on UK alcohol treatment trial (UKATT), social behaviour and network therapy compared to motivational enhancement therapy	CUA	Markov: Lifetime	Individual	Healthcare sector	The study used a cohort based probabilistic lifetime Markov model where alcohol consumption and drinking history are used for classifying patients into 5 Markov states: hazardous drinking, ex-hazardous drinking, harmful drinking, ex-harmful drinking, and death. Input parameters were derived from many literature. The main outcomes were QALYs and lifetime costs.

Table 2-3 Characteristic of 26 eligible economic modelling studies (cont.)

Author, year	Country	Study participants	Implementation levels	Intervention	Study type	Modelling approach: time horizon	level of consequence	Perspective	Summary of quality assessment
(Braithwaite et al., 2014)	Kenya	Kenya population	Population level	Cognitive behavioural therapy-based intervention	CEA	System dynamics: 20 years	Individual and others (population-level HIV transmission)	Healthcare sector	An impact of hypothetical interventions directed at unhealthy alcohol use on HIV infections and deaths was investigated. Input parameters were based on assumptions on intervention and evidence synthesis. The model calibration and validation were analysed. One-way sensitivity analysis was performed by varied effectiveness and ART nonadherence and STI prevalence.
(Brodtkorb et al., 2016)	The UK	Alcohol-dependent patients	Individual level	Nalmefene plus psychosocial support compared with psychosocial intervention alone	CUA	Markov: 5 years	Individual (crime, unemploye, and absent work)	Societal	A Markov model (five drinking states, five related conditions, and death) was constructed. Health-related and societal costs were drawn from public data and the literature. The individual risk event was employed from SAPM. One-way sensitivity and probabilistic sensitivity analyses (PSA) were performed. Quality-control procedure was confirmed by verifying of all input data.
(Byrnes et al., 2010)	Australia	Australian population	Population level	Volumetric taxation	CUA	Aggregate model /Multistate life table model: Lifetime	Individual	Healthcare sector	To model the potential benefits of volumetric taxation to alcohol consumption, data on cost and intervention effect were derived from the literature. The main health outcomes were DALYs. PSA was performed.
(Chisholm et al., 2004)	12 epidemiological WHO sub-regions of the world	12 WHO sub-regions population	Population level	Brief physician advice, taxation, roadside random breath testing, restricted sales access, and advertising bans	CUA	Aggregate model /State transition cohort population model: Lifetime	Individual	Healthcare sector	A population model was used to estimate the impact of four interventions aimed at reducing hazardous alcohol use. Population-level intervention effects were gauged in terms of DALYs. Model parameters were from the literature. Best and worst cases and PSA were performed.

Table 2-3 Characteristic of 26 eligible economic modelling studies (cont.)

Author, year	Country	Study participants	Implementation levels	Intervention	Study type	Modelling approach: time horizon	level of consequence	Perspective	Summary of quality assessment
(Cobiac et al., 2009)	Australia	Australian population	Population level	volumetric taxation, advertising bans, an increase in minimum legal drinking age, licensing controls on operating hours, brief intervention (with and without general practitioner telemarketing and support), drink driving campaigns, random breath testing and residential treatment for alcohol dependence (with and without naltrexone)	CUA	Aggregate model /Multi-state, multiple cohort life table model: Lifetime	Individual	Healthcare sector	Selected 8 interventions for reducing alcohol-attributable harm were compared and determined the optimal intervention mix. Health outcome was DALYs and adjusted under-reported alcohol consumption. Model parameters were from the literature. Sensitivity of key assumptions was investigated i.e. sustainability of intervention health effect over time.
(Ditsuwan et al., 2013)	Thailand	Thai population	Population level	Random breath testing, selective breath testing, and mass media campaigns, both current and intervention scenarios, were compared with a ‘‘do-nothing’’ scenario.	CUA	Decision tree: Lifetime	Individual and other (i.e. road traffic injuries’ victims)	Healthcare sector	To determine the cost-effectiveness of interventions to reduce road traffic injuries caused by driving under the influence of alcohol in Thailand, the model considered road traffic crash victims who were injured, disabled or died. Intervention effectiveness was derived from published reviews and a study in one province of Thailand. PSA was performed.
(Gentilello et al., 2005)	The US	Trauma patients treated in hospital and emergency department aged 18 and over	Individual level	Screening and brief alcohol intervention	CBA	Decision tree and Markov: 3 years	Individual	Healthcare sector	To determine if brief alcohol interventions in trauma centres reduce healthcare costs, the analysis was restricted to direct injury related medical costs only. Model parameters were retrieved from the literature and examined 1-way sensitivity and PSA.

Table 2-3 Characteristic of 26 eligible economic modelling studies (cont.)

Author, year	Country	Study participants	Implementation levels	Intervention	Study type	Modelling approach: time horizon	level of consequence	Perspective	Summary of quality assessment
(Holm et al., 2014a)	Denmark	Adult Danish population	Population level	Three different scenarios of changed taxation of alcoholic beverages in Denmark (20% and 100% increase and 10% decrease)	CUA	Aggregate model/ Multi-state population life table: Lifetime	Individual	Healthcare sector	Model structure was classified into healthy, diseases, and dead. The lifetime consequences were estimated as the difference in DALYs between current alcohol consumption and an identical population that changes their alcohol consumption due to changes in taxation. One-way sensitivity and PSA were performed.
(Holm et al., 2014b)	Denmark	Adult Danish population	Individual and population levels	30% increased taxation, increased minimum legal drinking age, advertisement bans, limited hours of retail sales, and brief and longer individual interventions	CUA	Decision tree: Lifetime	Individual	Healthcare sector	Potential consequences were evaluated as changes in incidence, prevalence and mortality of alcohol-related diseases and injuries using a multiple cohort, multi-state life table approach. Health outcome was measured in DALYs. One-way sensitivity testing model assumptions and PSA were performed.
(Kapoor et al., 2009)	The US	Adult men and women (aged 18-100 years) in primary care	Individual level	4 strategies for detecting unhealthy alcohol use in adult primary care patients: 1) questionnaire; 2) % Carbohydrate deficient transferrin (CDT); 3) questionnaire followed by %CDT if the questionnaire is negative; and 4) no screening	CUA	Decision tree and Markov: Lifetime	Individual	Societal	Model structure combined a decision tree (compared screening options) and Markov (defined by consumption and the presence of an alcohol use disorders). Model parameters were obtained from the literature and Medicare reimbursement data. Model calibration was performed by comparing transition drinking state with the published information. QALYs were measured. One- and two-way sensitivity analyses were used to assess the uncertainty of individual parameter value.

Table 2-3 Characteristic of 26 eligible economic modelling studies (cont.)

Author, year	Country	Study participants	Implementation levels	Intervention	Study type	Modelling approach: time horizon	level of consequence	Perspective	Summary of quality assessment
(Kessler et al., 2015)	East Africa	Persons living with HIV/AIDS as 4 different strategies for targeting intervention—(i) all HIV-infected persons attending clinic; (ii) only patients in the pre-antiretroviral therapy (ART) stages of care; (iii) only patients receiving ART; and (iv) only patients with detectable viral loads (VLs) regardless of disease stage.	Population level (HIV infection)	Screening for hazardous alcohol consumption using the AUDIT and offering the cognitive behavioural therapy (CBT)-based intervention to those who screened positive	CUA	System dynamics: 20 years	Individual and others (population-level HIV transmission)	Healthcare sector	The model simulated the course of the HIV epidemic over varying time horizons and tracked benefits of potential interventions. Outcome measured included number of infections averted, AIDS-related deaths averted, and QALYs. Model parameters were derived from the literature. Model calibration was analysed. One- and two-way sensitivity analyses were used to assess the uncertainty of individual parameter value.
(Lai et al., 2007)	Estonia	General population and at-risk drinker	Population level	Excise tax on alcoholic beverages; reduced access to alcoholic beverage retail outlets; a comprehensive advertising ban (TV, radio and billboards) on alcoholic products; roadside breath-testing for blood alcohol content in motor vehicle driver; and brief interventions involving counselling to at-risk drinkers by a primary care physician	CUA	Aggregate model/ WHO cost-effectiveness modelling: Lifetime	Individual	Societal	To evaluate the costs, health effects and cost-effectiveness of interventions to reduce smoking and hazardous alcohol use in Estonia based on locally available data. The study showed how to utilize existing WHO-CHOICE tools and adapt region level information down to the national level. DALYs was a health outcome. All interventions were compared to no intervention. Best and worse-case scenarios were used for uncertainty analysis.

Table 2-3 Characteristic of 26 eligible economic modelling studies (cont.)

Author, year	Country	Study participants	Implementation levels	Intervention	Study type	Modelling approach: time horizon	level of consequence	Perspective	Summary of quality assessment
(Laramee et al., 2014)	England and Wales	Alcohol-dependent patients with high/very high drinking risk levels	Individual level	Nalmefene combined with psychosocial support compared to psychosocial support alone	CUA	Markov: 5 years	Individual	NHS	To evaluate the public health benefit of reducing harmful alcohol-attributable diseases, injuries and death. Treatment effect was obtained from three clinical trials (1-year trial) of nalmefene. Baseline characteristics of the model cohort, resource utilisation, and utilities were also from those trials. Published epidemiological studies were used for modelling alcohol-related events occurring at different levels of alcohol drinking level. QALYs was measured. One-way and PSA were performed.
(Mortimer and Segal, 2005)	Australia	Problem alcohol drinker and alcohol dependence	Individual level	1) Brief interventions for problem drinking; 2) psychotherapy for mild to moderate dependence; and 3) drug-therapy adjuvant to counselling for detoxified patients with a history of severe physical dependence	CEA	Markov: Lifetime	Individual	Societal	The study used a time-dependent state-transition model to compare complementary and competing interventions for prevention or treatment of alcohol misuse and dependence; compares usual care with interventions. QALY was estimated. Model parameters were from the literature. Univariate sensitivity analysis was performed by varied cost and effectiveness.
(Navarro et al., 2014)	Australia	Risky drinkers who visit a community pharmacy annually in 10 rural communities	Community level	Current practice and nine possible scenarios with differences of 10%,20% and 100% either in screening or in BI or combination of both	CEA	Decision tree: 1 year	Individual	Provider	A decision model was developed to assess costs and changes in outcomes from pharmacist-delivered screening and BI on alcohol consumption using 1-year data from a survey. Outcome measure was risky drinker reducing alcohol consumption. One-way sensitivity analysis was analysed by varied effectiveness of alternative interventions.

Table 2-3 Characteristic of 26 eligible economic modelling studies (cont.)

Author, year	Country	Study participants	Implementation levels	Intervention	Study type	Modelling approach: time horizon	level of consequence	Perspective	Summary of quality assessment
(Navarro et al., 2011)	Australia	Risky drinkers in 10 rural communities in New South Wales	Individual level	Nine difference scenarios with incremental increase in screening, brief intervention, or a combination of screening and brief intervention was compared to the current practice.	CEA	Decision trees: 1 year	Individual	Healthcare sector	A decision model was developed to assess costs and changes in outcomes from pharmacist-delivered screening and BI on alcohol consumption using 1-year data from a survey. Outcome measure was risky drinker reducing alcohol consumption. One-way sensitivity analysis was analysed by varied effectiveness of alternative interventions.
(Neighbors et al., 2010)	The US	Alcohol-involved youth (aged 18-19) in the emergency department (ED)	Individual level	1) Assessment of alcohol status conducted by hospital staff during routine ED intake (standard screening); and 2) added procedures to proactively scan the ED for youth and solicit information about alcohol involvement (enhanced screening)	CEA and CUA	Decision trees: Lifetime	Individual and others (accident fatality related to medical, legal, administrative, property damage)	Provider and societal	A decision modelling was conducted using data - which were derived from an RCT (6-month follow up period). QALYs and social costs related to accident fatalities were estimated. One-way and PSA were conducted.
(Palmer et al., 2000)	Germany	Detoxified alcoholic patients	Individual level	1) Standard counselling therapy, and 2) standard counselling therapy with adjuvant accamprosate	CEA	Markov: Lifetime	Individual	Healthcare sector	The study used a Markov model to explore the long term clinical and economic outcomes of alcohol maintenance with counselling or counselling plus accamprosate. Data were obtained from the published literature. One-way sensitivity was used for test model assumptions.
(Purshouse et al., 2013)	England	Risky drinkers who are screened through GP's visits	Individual level	Universal alcohol screening and brief intervention programmes in primary care	CUA	Aggregate model /Sheffield Alcohol Policy Model (SAPM): 30 years	Individual	Healthcare sector	To develop a health economic model combining the healthcare resource requirements for alcohol screening and brief intervention with an epidemiological model of relationships between alcohol consumption and health harms. Health outcome was measured (i.e. QALYs). Sensitivity analyses were conducted by varied implementation options.

Table 2-3 Characteristic of 26 eligible economic modelling studies (cont.)

Author, year	Country	Study participants	Implementation levels	Intervention	Study type	Modelling approach: time horizon	level of consequence	Perspective	Summary of quality assessment
(Quanbeck et al., 2010)	The US	Adult population with an alcohol problem	Individual level	Screening, brief intervention, and referral to treatment (SIBRT)	CBA	Monte Carlo simulation model/individual-based micro-simulation: 4 years	Others	Employer	This study developed a cost-benefit model that includes the employer's perspective by considering the costs of absenteeism and impaired presenteeism due to problem drinking. No uncertainty analysis was performed.
(Smit et al., 2011)	The Netherlands	Alcohol use disorder	Population level	eHealth intervention: 1) 'DrinkTest' is a brief online intervention consisting of screening one's alcohol use by automated personalized advice; 2) 'DrinkingLess' is an online four-step cognitive behavioral intervention; and 3) an online therapist-led treatment for problem drinking, termed Online Treatment henceforth.	CUA	Alcohol model (ALCMOD): 12 months	Individual	Healthcare sector	To estimate the cost-effectiveness of competing healthcare systems in curbing alcohol use at the national level. This was illustrated for scenarios where new eHealth technologies for alcohol use disorders were introduced in the Dutch healthcare system. ALCMOD assessed short-term (12-month) DALYs and healthcare budget impact. Probabilistic model was presented using ALCMOD.
(Tariq et al., 2009)	The Netherlands	Risky drinkers aged between 20 and 65 who visit GP yearly (50%)	Individual level	Opportunistic screening and brief intervention for at-risk drinkers	CUA	Markov: 80 years	Individual	Healthcare sector	The study used the RIVM Chronic Disease Model (CDM) to conduct a CEA of screening and brief intervention for alcohol in primary care targeting at risk drinkers. Outcome measured was QALYs. PSA was performed.
(Zur and Zaric, 2016)	Canada	General population aged 17 years and over	Individual level	SBI (screening tools were AUDIT and AUDIT-C) in the primary care setting compared to No SBI	CUA	Microsimulation (100,000,000 individuals): Lifetime	Individual	NHS	The study developed a microsimulation model to estimate the consequences of SBI in the primary care setting. Drinking states were classified as lifetime abstainer, former drinker, drinker, and death. Binge drinking was also incorporate when determining average alcohol consumption per year. Model calibration was performed to compare alcohol consumption to a survey.

2.5.3 Measurement and valuation of consequences

The majority of the eligible studies modelled intermediate and longer-term health consequences including alcohol consumption status, alcohol-related diseases and death. These health outcomes were eventually converted into life years, QALYs, and DALYs (Angus et al., 2014b, Barbosa et al., 2015, Barbosa et al., 2010a, Byrnes et al., 2010, Chisholm et al., 2004, Cobiac et al., 2009, Holm et al., 2014b, Holm et al., 2014a, Kapoor et al., 2009, Kessler et al., 2015, Lai et al., 2007, Laramee et al., 2014, Purshouse et al., 2013, Smit et al., 2011, Tariq et al., 2009, Zur and Zaric, 2016). Non-health consequences of individual drinkers were also included in two studies e.g. crime, unemployed, and income loss (Barbosa et al., 2015, Brodtkorb et al., 2016). In addition, alcohol-related consequences to others were measured in two studies in terms of social costs (e.g. accident fatalities related to medical, legal, administrative, and property damage), and health consequences of drink-driving's victims (Ditsuwan et al., 2013, Neighbors et al., 2010). Almost all of the studies employed the healthcare sector perspective (n = 20), and only six studies used societal as the analytical perspective. The perspective used for analysis identifies the cost that are only considered as relevant to such perspective.

2.5.4 Other economic evaluation components

The economic models used in previous literature were constructed as 'drinking states' to examine the average levels of consumption (e.g. absenteeism, low risk, moderate risk, and high risk consumptions) and alcohol-related diseases classified by drinking levels (Barbosa et al., 2015, Barbosa et al., 2010b, Purshouse et al., 2013, Cobiac et al., 2009). The models can be used to estimate only the consequences based on average consumptions; however, there was only one study that considered episodic heavy drinking or binge drinking which was only considered a factor in death due to injury (Zur and Zaric, 2016).

Sensitivity analyses were mostly conducted to examine the uncertainty of cost-effectiveness results. PSA (see detailed Appendix 8) and one-way sensitivity analyses were typically used (Angus et al., 2014a, Barbosa et al., 2015, Barbosa et al., 2010b, Braithwaite et al., 2014, Brodtkorb et al., 2016, Byrnes et al., 2010, Chisholm et al., 2004, Holm et al., 2014b, Holm et al., 2014a, Laramee et al., 2014, Neighbors et al., 2010, Smit et al., 2011, Tariq et al., 2009). Best and worse-case scenarios were also conducted based on specific research questions such as varied implementation options (Cobiac et al., 2009, Kapoor et al., 2009, Kessler et al., 2015, Lai et al., 2007, Mortimer and Segal, 2005, Navarro et al., 2011, Navarro et al., 2014, Palmer et al., 2000, Purshouse et al., 2013). In addition, model calibration for internal consistency was also conducted and compared to baseline country-specific alcohol consumption and alcohol-related epidemiology (Braithwaite et al., 2014, Kapoor et al., 2009, Kessler et al., 2015, Zur and Zaric, 2016). No external consistency was performed in the included studies.

In addition, self-reporting alcohol consumption was often used for measuring behaviour change due to receiving alcohol intervention, whereas the assessment of self-reported alcohol consumption indicated deliberate under-reporting. Nevertheless, there were limited cost-effectiveness studies that adjusted for under-reporting of alcohol consumption (Chisholm et al., 2004, Cobiac et al., 2009). The adjustment led to improvements in cost-effectiveness for some interventions: population-wide interventions (taxation, advertising bans and licensing controls on operating hours) improved most, and targeted interventions (brief intervention and residential treatment with naltrexone) improved slightly but interventions based on reductions in road traffic accidents rather than reported consumption (increasing the minimum legal drinking age, drink driving mass media and random breath testing) were not effective. Overall, the adjustment did not alter the order of interventions in the optimal intervention mix.

2.6 Discussion

2.6.1 Evidence gap of modelling cost-effectiveness in alcohol interventions

There are various methodological challenges related to developing an economic evaluation of alcohol intervention using modelling approaches. To tackle a range of alcohol-related consequences and alcohol intervention effects, these challenges should be considered. Firstly, the evidence of effectiveness derived from RCTs was not appropriate for alcohol interventions such as pricing policy, drink-driving policy, and law enforcement (e.g. random breath testing of drivers). Thus, intervention effectiveness for previous modelling studies were obtained from published studies (i.e. the change in consumption, and the relationships of consumption level and alcohol-related harms occurring at different consumption levels); however, this may lead to the potential for bias and/or confounding in the underlying studies of effectiveness (Byrnes et al., 2010, Chisholm et al., 2004, Cobiac et al., 2009, Holm et al., 2014b, Holm et al., 2014a, Ditsuwan et al., 2013, Bye, 2007). Even though measured alcohol consumption at the individual level was assessed to be intervention's effectiveness, the adjustment under-reporting consumption was just presented in a few studies (Chisholm et al., 2004, Cobiac et al., 2009). Moreover, the mathematical model that gathered multiple sources of evidence on a range of parameters to estimate the costs and outcomes, so this may possibly increase the degree of parameter uncertainty (Appendix 8).

Secondly, the most common modelling approaches were decision tree and Markov model using the incidence-based approach and QALY (or DALY) framework. This was due to the objectivity of healthcare decision-making to compare across different alcohol policies and interventions with country-specific thresholds (Brodtkorb et al., 2016, Byrnes et al., 2010, Cobiac et al., 2009, Ditsuwan et al., 2013, Holm et al., 2014b, Holm et al., 2014a, Purshouse et al., 2013). Using these methods, there were three main issues related to modelling over time horizon which were broadly discussed: 1) the change of

drinking status over time, 2) the time lag between alcohol consumption changes and changes in its related harm; and 3) the morbidity and mortality incidence data over time. These issues required longitudinal data on individuals' drinking patterns and their alcohol-related consequences - which was not readily available in many study settings.

Thirdly, existing studies constructed health state transition model based on average drinking levels to describe the plausible consumption within the cohort e.g. abstainer, low-, moderate- and high- consumption levels; each level applied the risk of potentially relevant events. The relative risk of alcohol-related consequences - which are commonly defined as alcohol-attributable conditions – were roughly classified based on a few average consumption levels based on availability of evidence (Grant et al., 2009, Jones and Bellis, 2014, Jones et al., 2008, Kendler et al., 2016, Rehm and Roerecke, 2013, Roerecke and Rehm, 2013). Nevertheless, there was a lack of modelling studies that considered heavy episodic drinking to be a drinking state that causes acute alcohol-related conditions, e.g. accidents and injuries.

Finally, there were no included studies which addressed health equity in their evaluations. However, the effects on health inequalities were conducted from effectiveness studies using the Sheffield Alcohol Policy Model which stratified the impacts of taxation and price policies by lower income group and socioeconomic status (Meier et al., 2016, Holmes et al., 2014a). The reduction of health inequality has been an area of interest for public health policy research. Particularly, lower SES has been associated with higher mortality for alcohol-attributable causes – despite lower socioeconomic groups often reporting lower average levels of alcohol consumption defined as the Alcohol Harm Paradox (Smith and Foster, 2014). Thus, it is desirable if an economic evaluation of interventions introduced by public health researchers is able to assess the impact on inequalities.

Cookson and colleagues proposed four methods for considering inequality and equity within economic evaluations of public health interventions (Cookson et al., 2009): 1) identification of relevant equity considerations and a review of existing literature to provide qualitative discussion on equity issues; 2) quantitative analysis of key subgroup data from trials, where available, around the impact of the intervention upon health inequities; 3) estimating the opportunity cost of including equity considerations in terms of health foregone (i.e. the comparison of health foregone if adopting the equitable option with that of maximising health); and 4) valuing health inequality reduction by quantitatively weighting health outcomes according to equity considerations. However, there is currently no agreement over the most appropriate approach.

However, there were also limitations of the reviews to find the evidence gaps. First, the review did not conduct an exhaustive search of the grey literature. The results relied on published, peer-reviewed studies reported in English-language journals. Second, screening titles and abstracts may have neglected some articles for which economic evaluation results would have been reported in the results section. Finally, publication bias would have likely occurred due to cost-effective interventions tend to be published. Further review to explore the knowledge gap of evaluation methods should comprehensively search grey literature such as theses, evaluation reports, and methodological reports.

2.6.2 Rationale of developing current alcohol intervention model for cost-effectiveness analysis

In this study, an alcohol intervention model will be developed to evaluate the costs, outcomes, and cost-effectiveness of alcohol interventions to inform healthcare policy-making. To produce a cost-effectiveness result that can be compared to the ceiling threshold, this current alcohol intervention model will apply the QALY framework (National Institute for Health and Care Excellence (NICE), 2012). Although alcohol consumption can cause wider effects in terms of both non-health consequences and harms to other, this current

study will not capture them. In response to the challenges of modelling heterogeneity cohort (e.g. differentiated by age and risk behaviours) and its consequences on health outcomes and relevant costs, individual-level input data and modelling techniques were required (Caro et al., 2010). These issues required longitudinal data on individuals' drinking patterns and their alcohol-related outcomes and costs - which is not readily available in many study settings. Thus, the model input parameters will be retrieved from a single longitudinal dataset (Scottish linkage dataset as described in Chapter 3) at the individual-level; data needed for developing all the component parts of the decision-analytic model (e.g. baseline risk classified by alcohol consumption in terms of the AUDIT score and binge drinking, morbidity and mortality incidence data over time, health related quality of life, and healthcare costs) to determine the impact of these factors on health outcomes, by age and risk profiles, were also retrieved from this dataset.

The AUDIT score measured in the Scottish Health Surveys (SHeS) will be used for classifying drinking states in the analysis so the estimated plausible range of alcohol-related consequences can be classified based on many levels of drinking consumption. This is because the AUDIT has become the gold standard for screening for alcohol use disorders in the UK (National Collaborating Centre for Mental Health, 2011) and many other countries including Thailand (Dybek et al., 2006, Gache et al., 2005, Babor et al., 2001, Pradhan et al., 2012, Kawada et al., 2011, Li et al., 2011, Areesantichai et al., 2010, Assanangkornchai et al., 2010). Moreover, the Thai public health and health promotion policy-makers are considering adopting the screening and treatment for alcohol use disorders, and they are monitoring the magnitude of alcohol use disorder among the Thai population using routine national health surveys (Aekplakorn et al., 2015). In addition, the AUDIT was frequently used as the outcome measure in existing alcohol intervention studies (McCambridge and Day, 2008, Kaner et al., 2013, Shiles et al., 2013). This is the first study which explores the association of the AUDIT score and alcohol morbidity and mortality. Moreover, according to the under-reporting bias of alcohol

consumption surveys (Babor et al., 2010a, Meier et al., 2013, Boniface and Shelton, 2013), this study will adjust under-reported alcohol consumption among survey participants using alcohol sales data and incorporate this into the cost-effectiveness analysis (HM Revenue and Customs, 2012, Robinson et al., 2013) as this was lacking in the previous economic modelling study.

In addition, other behaviours that often cluster or co-occur within individual drinkers will be allowed to influence potentially relevant consequences of study cohorts, i.e. smoking status (Aekplakorn et al., 2008, De Leon et al., 2007, Falk et al., 2006, Harrison et al., 2008, McKee et al., 2010), physical activity (Kendzor et al., 2008), and body mass index (Hart et al., 2010). Including these modifiable behaviours in alcohol model has not been applied in the previous alcohol modelling study due to a lack of comprehensive health behaviour at the individual-level. Finally, the current model will consider health inequality and equity issues by including the standard measurement of socioeconomic status (Scottish Index multiple deprivation: SIMD) in all analyses (Cookson et al., 2009, Office of the Chief Statistician, 2004).

Furthermore, this study proposes to transfer the developed alcohol intervention model in Scottish setting to the Thai setting. Alcohol consumption and related-harm in Thailand has also increased steadily in the past decade, although still lower than in most Western countries (Rehm et al., 2009, Whiteford et al., 2013). Similar to Scotland, alcohol drinking problems were found, especially with men living in the most deprived areas in Thailand; approximately half of young men reported binge drinking behaviour, leading to high rates of acute alcohol-related harms such as accidents and violence (Aekplakorn et al., 2008, Assanangkornchai et al., 2010, Beeston C et al., 2014, Rehm et al., 2009). In addition, Thailand has widely applied the translated and validated the AUDIT in both health care setting and national health surveys for many years (Aekplakorn et al., 2015, Assanangkornchai et al., 2010). Based on these contextual factors, the adaptation approach of the Scottish model was possible by comparing population alcohol-related problems and AUDIT scores between two settings.

Chapter 3: Conceptual framework and data sources

3.1 Introduction

This chapter will describe the conceptual framework of this study via five main points. Firstly, a conceptual framework of the alcohol intervention evaluation will illustrate how to evaluate intervention effectiveness using intermediate outcomes to predict the final outcomes of interest, i.e. life years (LYs), quality-adjusted life years (QALYs), and lifetime healthcare costs. To demonstrate the predictive ability of selected surrogate indicators, this study developed an alcohol intervention model to show how these surrogate outcomes can accurately predict the final outcomes (to be explained in the following parts). Secondly, the study objectives and analytical framework are described to outline the data set and stages of approach used for developing the model. Thirdly, the model of alcohol-related harms used for estimating LYs, QALYs, and costs is shown in the form of a health state transition model, and details how the health states were identified. Fourthly, the key data source used for the input parameters of the developed alcohol intervention model are identified. Lastly, ethical issues related to the population sample recruited in this study are also raised.

3.2 Conceptual framework of alcohol control programme evaluation

Figure 3-1 presents a conceptual framework of the alcohol intervention model adapted from the Biomarkers Definitions Working Group 2001 (Biomarkers Definitions Working Group, 2001, Buyse et al., 2010). The biomarker measurements (as compared to risk behaviour in this study) can help explain the empirical results of clinical trials by investigating the relationship between the effects of interventions on molecular and cellular pathways and

overall clinical responses. The biomarkers that represent highly-sensitive and specific indicators of disease pathways have been used as substitutes for the final outcomes in clinical trials when evidence indicates that they predict clinical risk or benefit. An alcohol intervention would have direct and indirect effects on a wide range of an individual drinker's modifiable risk factors such as changing alcohol drinking patterns and other related risk behaviours (e.g. number of cigarettes per day). Consequently, the mathematical analyses revealed that the subset of those risk factors represented in the figure by a quadrant could achieve surrogate endpoint status in terms of accuracy (correlation of measure) and precision (reproducibility) - which is required to be reasonably likely to predict an endpoint such as alcohol-related hospitalisation and death. These outcomes can then be converted to LYs, QALYs, and long-term costs, and intervention cost-effectiveness can subsequently be estimated.

The alcohol intervention model was structured using a health state transition model to characterise the plausible consequences (i.e. hospitalisation and death) of different drinking behaviours (as described in section 3.6). The model was developed using the key features of economic evaluation such as perspective, time horizon, and measured costs and outcomes (Briggs et al., 2006c, Drummond MF et al., 1997, Gray et al., 2011a). Afterward, LYs, QALYs and lifetime economic costs can be estimated and categorised by alcohol drinking patterns. The estimated health outcomes and costs of different levels of drinking risks are able to show the consequences of alcohol drinking. Then, cost-effectiveness can be compared between the new alcohol intervention -which changes the risk of alcohol drinking from the baseline to the existing intervention. These estimated outcomes are widely recommended for the purpose of conducting economic evaluations of health interventions to inform policy-making (ISPOR, 2014, NICE, 2013, Chaikledkaew and Kittrongsiri, 2014, Teerawattananon and Chaikledkaew, 2008).

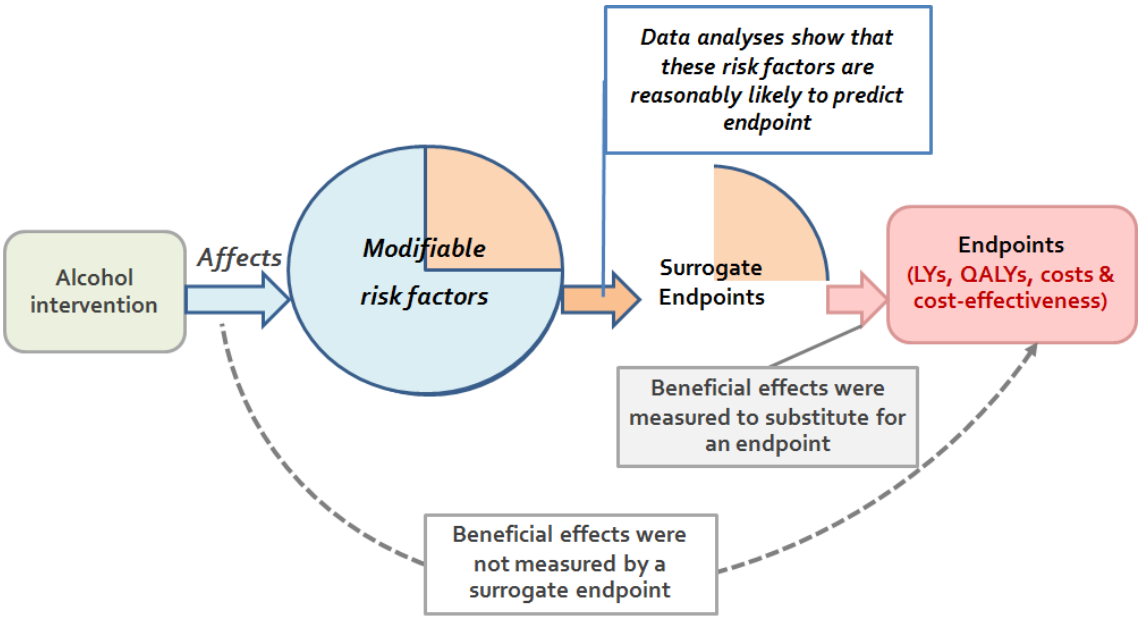


Figure 3-1 Conceptual framework of the alcohol intervention model which signifies the relationship between alcohol intervention and its measured effects on modifiable risk factors, surrogate endpoints, and endpoints
*adapted from the (Biomarkers Definitions Working Group, 2001)

3.3 Study objectives

1. To investigate hospitalisations and deaths among alcohol drinking patterns classified by the Alcohol Use Disorder Identification Test or AUDIT (Babor et al., 2001) as well as to examine the relationship between alcohol-related harms and other related risk factors e.g. socioeconomic status and smoking.

2. To develop an alcohol intervention model for the estimation of LYs, QALYs, and lifetime costs of different alcohol drinking patterns inclusive of those other risk factors so the model can be used for further economic evaluation of alcohol policies and interventions to inform policy-makers.

3. To develop a protocol of methodological transferability to other settings.

3.4 Analytical framework of this study

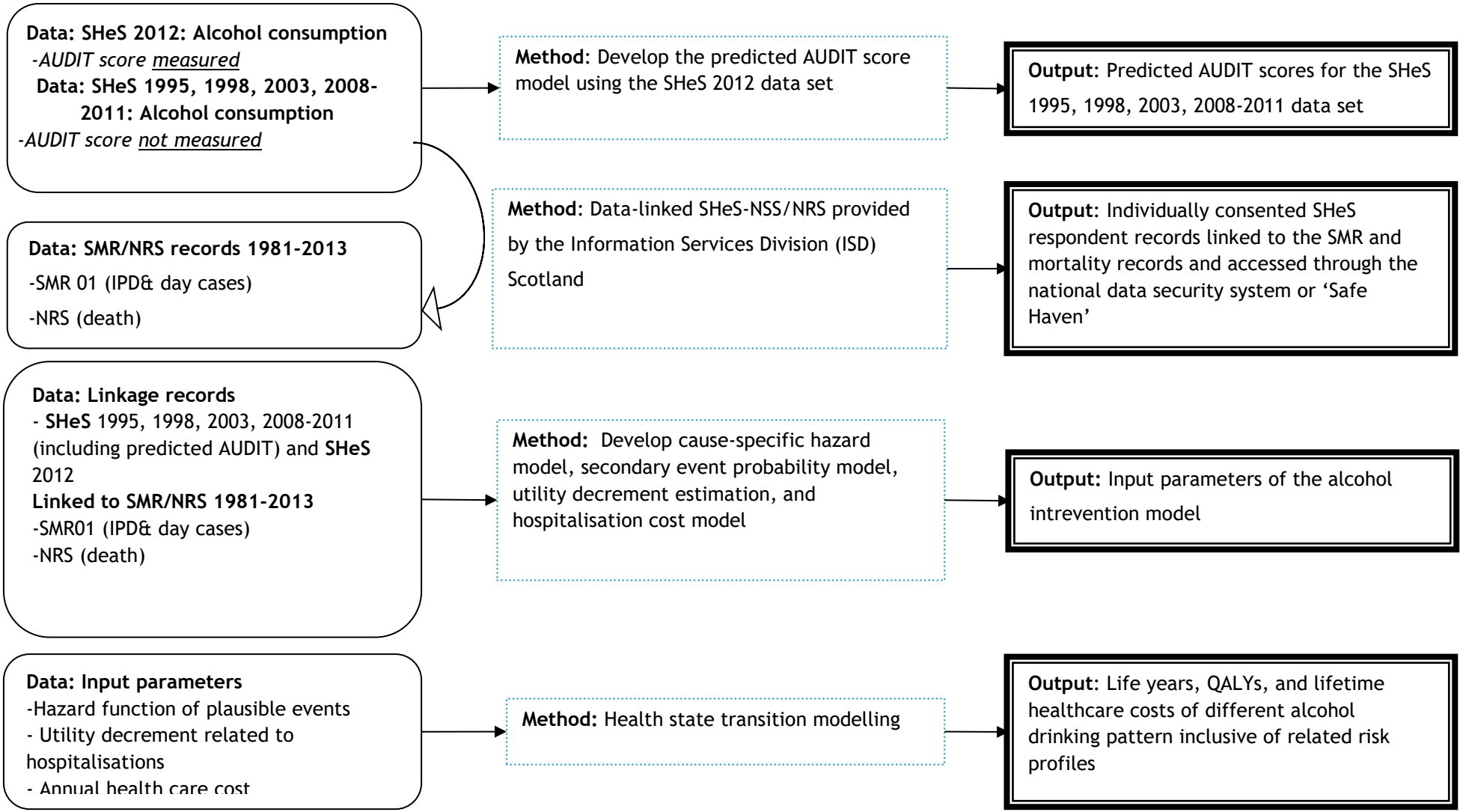
An analytical framework of this study is illustrated in Figure 3-2. The first stage of analysis consisted of assessing how alcohol drinking status was measured in the Scottish Health Surveys cohorts (SHeS). A variation of alcohol drinking assessments among survey years was observed. CAGE questionnaires combined with weekly unit alcohol consumption were included to assess a potential problem drinking in the SHeS from 1995-2011. However, CAGE has been excluded from the alcohol consumption questionnaire since 2012 and replaced by the AUDIT. The AUDIT questionnaire was developed to define alcohol use disorder in terms of hazardous, harmful, and probable dependence based on the WHO ICD-10 definition(as described in Chapter 1) (World Health Organization, 1993). Nowadays, the AUDIT has been widely validated and recommended for alcohol use disorder screening and treatment in the primary healthcare setting in the UK (National Collaborating Centre for Mental Health, 2011) and translated into many languages including a Thai version (Dybek et al., 2006, Gache et al., 2005, Babor et al., 2001, Pradhan et al., 2012, Kawada et al., 2011, Li et al., 2011, Areesantichai et al., 2010, Assanangkornchai et al., 2010). . Moreover, the Thai public health and health promotion policy makers are considering to adopt the screening and treatment programmes for alcohol use disorders, and they are monitoring the magnitude of alcohol use disorder among Thai population using routine national health survey (Aekplakorn et al., 2015). This can be seen that using AUDIT seems to be suitable for this current study which ultimately aims to inform these policy makers who are focussing on drinker with alcohol use disorder rather than alcohol consumption volume in general.

Thus, the use of the AUDIT score for modelling can extrapolate the health impact caused by alcohol use disorders which are generally defined as the same WHO ICD-10 across countries (World Health Organization, 1993). The AUDIT score measured in the SHeS was used for classifying drinking states in the analysis so the estimated plausible range of alcohol-related consequences can

be classified based on many levels of drinking consumption. This would be an advantage to adapt the current model to other jurisdictions where the AUDIT is applied in both the healthcare setting as well as in general population survey for estimating alcohol use disorder prevalence (Aalto et al., 2009, Knibbe et al., 2006, Assanangkornchai et al., 2010). Ideally, the AUDIT would have been used for all SHeS survey waves; to work around this issue, the AUDIT scores of the SHeS from 1995-2011 were predicted using a statistical model developed from the SHeS 2012 data set. The development of the AUDIT score prediction model will be described in Chapter 4:.

In the next stage, The data linkage element has contributed to estimate the input parameters needed for the health state transition model (Figure 3-3) as follows: 1) the cause-specific hazard function of alcohol-related harms as well as non-alcohol related harms as described in Chapter 6; 2) the utility decrement related to hospitalisations (see details in Chapter 5) for QALY estimation as described in Chapter 7; and 3) the modelling healthcare costs used to predict lifetime costs as described in Chapter 7. Moreover, the linkage of survey and hospitalisations has allowed the modelling approach to identify SHeS cohorts with no prior alcohol-related hospitalisation and develop an incidence-base model.

Figure 3-2 Analytical framework of this study



3.5 Health state transition model structure

The overall purpose of a health state transition model structure is to characterise the plausible consequences in a way that is appropriate for the decision problems and boundaries of the model (Briggs et al., 2006c, Drummond MF et al., 2005, Gray et al., 2011a, Roberts et al., 2012, Siebert et al., 2012). The first step in the development of the analytical model for alcohol intervention is the selection of the type of model as mentioned in Chapter 1 (Barton et al., 2004, Brennan et al., 2006). The choice about type of model and its structure complexity is always a trade-off between descriptive realism and tractability in terms of computational burden and data requirements (Briggs et al., 2016). The selected type of model and model structure was developed based on the three main reasons listed below.

Firstly, the chosen structure focussing on health state transition was employed for estimates of expected costs and effects in the health sector, and health states were based on recent evidence of the relationship between alcohol consumption and the risk of alcohol-related conditions and death (Jones and Bellis, 2014, Jones et al., 2008, Grant et al., 2009). Moreover, other plausible health statuses such as non-alcohol related condition were included to capture all relevant following events which could possibly occur over the follow-up period.

Secondly, non-health consequences (e.g. including crime and unemployment) and harm to others were not taken into account due to the limited study duration and accessibility of data. Hence, a cross-sectoral model was not considered, and this study could probably apply either a cohort model or an individual simulation model with no interaction (Barton et al., 2004, Brennan et al., 2006). When comparing both models, individual simulation models would be more time-consuming to develop and run so a multistate life table was used with a cohort Markov model to simulate multiple diseases including hospitalisations and death over lifetime. Moreover, the input

parameters of the cohort model were derived from analysing individual-level linked health data which could generate a wide range of subpopulation results differentiated by age, gender, and risk profiles as recorded in the linkage data.

Finally, the other objective of the developed alcohol intervention model is to transfer it to Thai setting so the main components of this study were determined through consultation with Thai alcohol research experts (Appendix 7). These experts agreed with the methodology including model structure, applying the AUDIT - which is commonly used for alcohol problem screening in the health-care setting as well as in the national health surveys, and possibility of using available health data in Thailand to adjust the Scottish model. According to the limited study period and data sources in Thailand, the completed transferability of this study to the Thai context would likely need a further study in Thailand.

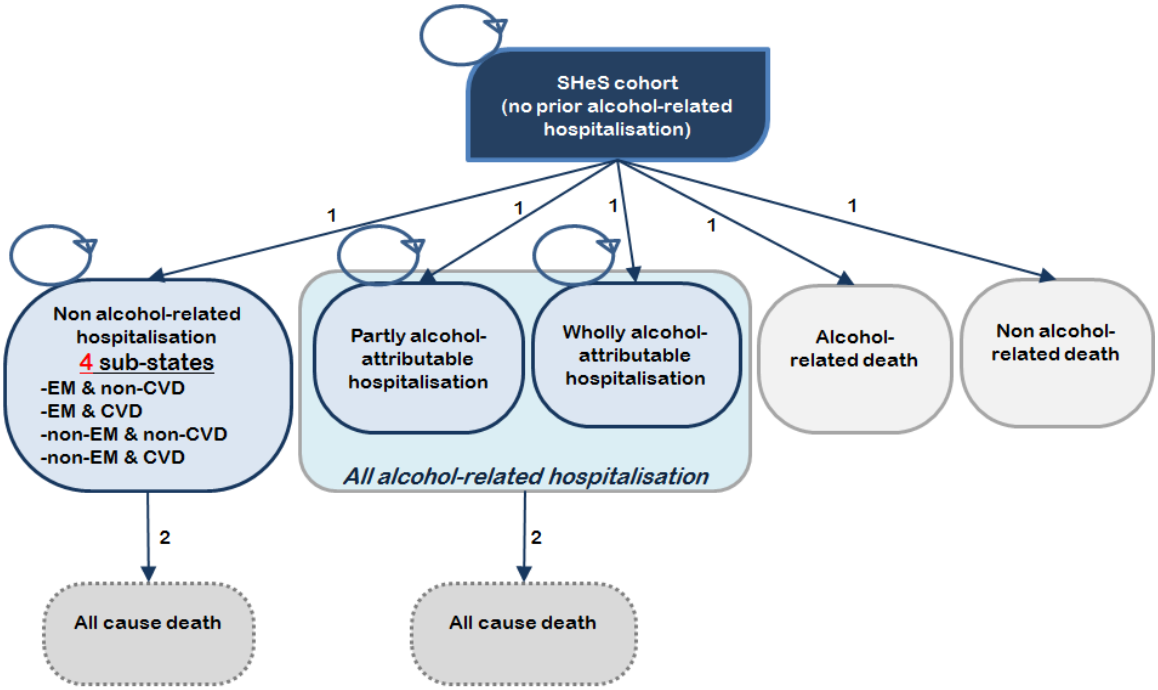
An incidence-based approach was applied for people who have never had alcohol related condition (from 1981 to 2013) to simulate the further health impact of alcohol drinker using survival analysis classified by individual risk factors e.g. age, sex, socioeconomic status and multiple alcohol-related factors (i.e. smoking, physical activity and BMI). Then, these factors were used for cause-specific hazard model of first competing events (hospitalisation and death). Time lag effect was dealt with time-to-first event analysis. However, alcohol consumption and other health behaviours can change over time, which the change of individual risk behaviours could not be captured in a cross-sectional health survey. The analysis could not define whether people have drunk heavily for many years or have started recently. However, the former drinker with alcohol-related condition is unlikely because the analysis included in particular of people who have never had alcohol related condition. Thus, the key assumption of study cohort for individual risk behaviours (i.e. alcohol consumption and related behaviours) was that their behaviours were stable over time within same age group classified by gender. The individual risk profiles including these factors were defined based on survey participants'

characteristics as varied by age and gender. The generated risk profiles modelled the consequences over lifetime. For a death event that was not the first event, selected modifiable risk factors were not included in the survival analysis, and age at first hospitalisation, sex, SIMD, and chronic conditions (at baseline) were used for modelling risk of death after the first hospitalisation as presented in equation 2 (Figure 3-3).

The disease states included in the alcohol model were derived from existing meta-analyses of data describing the relationship between alcohol consumption and the risk of alcohol related conditions as classified to be wholly- and partly-alcohol attributable conditions as identified by the alcohol-attributable fraction (AAF) (Jones and Bellis, 2014, Jones et al., 2008, Grant et al., 2009). For wholly alcohol-attributable morbidity and mortality, i.e. no cases would exist in the absence of alcohol consumption, AAF was assigned a value of 1, whereas partly alcohol-attributable conditions, i.e. a proportion of cases that could be avoided in the absence of alcohol, was given a score between 0 and 1. Using SHeS-SMR/NRS linkage dataset at individual-level, the selected covariates related to individual SHeS cohort were derived from eight survey years; they included the age at survey date, gender, SIMD, alcohol consumption including the AUDIT score and binge drinking, smoking status (i.e. the number of cigarettes per day), self-reported health condition (i.e. having CVD and diabetes), physical activity, and BMI. These covariates were included in the risk functions of competing first events after survey date defined by SMR records for hospitalisation and NRS records for death (as shown in equation 1 Figure 3-3). In addition, following hospitalisations and death after first hospitalisations were modelled using covariates i.e. age at first hospitalisation, CVD condition (Y/N), diabetes (Y/N), and SIMD quintile (as shown in equation 2 Figure 3-3).

The study cohort consisted of general population survey participants who had never experienced an alcohol-related hospitalisation prior to the survey date. Then, the risk of competing first events after the interview date of those

participants was simulated and classified by the SHeS baseline risk profiles as mentioned above (as shown in equation 1 Figure 3-3). Moreover, other non-alcohol related hospitalisations and deaths were taken into account to be competing first events after the survey date, and these events were states categorised into four categories by emergency/non-emergency admission - where the relevant cost and health outcome would be different - and cardiovascular diseases (CVD)/non-CVD as defined by ICD-9 and ICD-10 codes (Appendix 1). These combinations were set up to focus on the association between alcohol consumption and CVD (excluded CVD categorised as a partly alcohol-attributable condition). CVD was included due to the controversy of risks and benefits of alcohol consumption on CVD (Rehm et al., 2010a, Holmes et al., 2014b).



Equation 1: Function (age at survey date, alcohol drinking status at survey date i.e. AUDIT (0-40) & binge drinking (Y/N), cigarettes per day, CVD condition (Y/N), diabetes (Y/N), general health condition (GHQ score), physical activity, BMI, Prior other hospitalisation, SIMD) subgroup by gender
Equation 2: Function (age at first hospitalisation, CVD condition (Y/N), diabetes (Y/N), SIMD) subgroup by gender

*SHeS: Scottish Health Survey, EM: Emergency admission, CVD: Cardiovascular disease, SIMD: Scottish index of multiple Deprivation

Figure 3-3 Structure of the health state transition model

Figure 3-3 presents the modelled health state of alcohol-related hospitalisation and death of participants with no prior alcohol-related hospitalisation at the SHeS survey date (total cohort size of 46,230 comprising 20,729 males and 25,501 females). There were eight competing first events for the primary diagnosis after the survey date classified by ICD-9 and ICD-10: 1) wholly alcohol-attributable hospitalisation (21 conditions); 2) partly alcohol-attributable hospitalisation (26 conditions); 3) alcohol-related death defined as an alcohol-related hospitalised patient who died within 28 days; 4) non-alcohol related death defined as a non-alcohol related hospitalised patient who died within 28 days; 5) non-emergency (EM) admission and non-cardiovascular disease (CVD); 6) non-EM admission with CVD; 7) EM admission and non-CVD; and 8) EM admission with CVD (Jones and Bellis, 2014, Jones et al., 2008, Grant et al., 2009). Although the health state transition model (Figure 3-3) showed only first hospitalisation and death, the subsequent hospital admissions were part of the model, and the risk of having subsequent admissions were contributed to estimate QALY (reduction of HRQoL or dis-utilities) and total hospitalisation costs. The follow-up time for each participant was defined as the time from the interview date until either the date when the competing event occurred or until 31st December 2013 (censoring date).

After first hospitalisations, the risk of following hospitalisations and all-cause death were modelled and classified by age at first hospitalisation, CVD condition (Y/N), diabetes (Y/N), and SIMD quintile as shown in equation 2 (Figure 3-3). The after first hospitalisation event analysis considered following admissions and death after patients experienced the first hospitalisation, and this was divided into two groups: 1) hospitalised patients who had first alcohol-related hospitalisation after the survey date (either wholly or partly alcohol-attributable hospitalisation); and 2) hospitalised patients who had first non-alcohol related hospitalisation after the survey date. Thus, the follow-up time for each hospitalised patient was defined as the date of first hospitalisation until either the date of death or until 31st December 2013 (censoring date). Accordingly, it was found that there were differences in alcohol drinking

patterns and risks related to alcohol consumption between males and females (Schulte et al., 2009, Probst et al., 2015b, Richman et al., 1995). As such, males and females were modelled separately for all analyses.

3.6 Data identification

3.6.1 Scottish Health Survey (SHeS)

This study used the Scottish Health Survey (SHeS), which is a cross-sectional clustered, stratified multi-stage sample design. The SHeS aims to estimate the prevalence of health conditions and health-related behaviours and to monitor trends in the population's health over time (Dong and Erens, 1997, Shaw et al., 2000, Bromley et al., 2005, Bromley et al., 2009, Bromley et al., 2010, Bromley and Given, 2011, Bromley et al., 2012, Rutherford et al., 2013b). Thus, the surveys were carried out in 1995, 1998, 2003, and annually from 2008 onwards. The survey respondents are a representative sample of the Scottish population living in private households in Scotland. The age range for the 1995 wave was adults aged 16 to 64 years old. In the 1998 wave, the age range was extended to people aged between 2 and 74 years old. From 2003 onwards, the age range included children aged 0 to 15 and adults aged 16 years old and over as well. All analyses of this study particularly included adults aged 16 years and over since their alcohol consumption were measured, i.e. weekly unit alcohol consumption (units/week), unit consumed on the heaviest day, and the AUDIT (2012 only).

Topics included in the survey are core questions (i.e. dental health, general health, and mental well-being) and measurements, i.e. BMI (derived from weight and height), blood pressure, waist circumference, urine and saliva samples, as well as modules of self-reported specific health conditions and related risk factors, e.g. alcohol consumption, smoking, diet, physical activity, and obesity. In particular, since the SHeS from 2012 onwards measured participants' AUDIT scores, predicting AUDIT score models for the SHeS 1995-

2011 was done using other potential covariates, i.e. age, marital status, parental status, weekly unit alcohol consumption (units/week), unit consumed on the heaviest day (units/day), smoking status, general health condition (GHQ score), long-term condition (having cardiovascular condition), equivalised income, Scottish Index of multiple Deprivation or SIMD quintile (Office of the Chief Statistician, 2004), NSSEC of household reference person (five groups professional), NSSEC of parental (five groups professional and selected highest level compared between parents), economic activity, and highest educational qualification; these covariates were analysed sub-grouped by gender. The predicted AUDIT score will be described in Chapter 4.

Additionally, this study also investigated alcohol-related harms caused by binge drinking, i.e. heavy episodic drinking. However, since there is no standard definition of binge drinking in the UK, the SHeS uses the Health Survey for England and the General Lifestyle Survey's definition (Lifestyle Statistics of Health and Social Care Information Centre, 2014, Office for National Statistics, 2013) to enable comparisons between the SHeS and other major surveys of alcohol consumption in Britain. Both these surveys define binge drinking as consuming more than six units in one occasion for women and more than eight units for men (Rutherford et al., 2013a). In the UK, one unit is equivalent to one shot of a spirit, a glass of wine, or half a pint of beer. SHeS participants who are current drinkers were also interviewed to determine the number of units consumed on the heaviest day in the past seven days; this would be used to classify whether the drinker would qualify as a binge drinker.

3.6.2 Scottish Morbidity Records and National Records Scotland (SMR/NRS)

The SMR data set is currently held by the Information Services Division (ISD) of the National Health Services Scotland (Information Services Division, Fleming et al., 2012). The SMR hospital records include: SMR00 Outpatient Attendance; SMR01 General/Acute Inpatient & Day Case; SMR02 Maternity

Inpatient & Day Case; SMR04 Mental Health Inpatient & Day Case; and SMR06 Cancer Registration. The SMR also holds data on mortality in Scotland from the NRS. SMR data includes patients' personal information, demographic details, and information on health conditions. The diagnoses of patients' health condition are identified by the ICD-9 (prior to 1996) and ICD-10 (1996 onwards). The data held in the SMR system links each patient's various records together via the Scottish Record Linkage System; this system is in place to ensure the record linkage is done accurately. Due to errors in recording, exact matchings between records can miss up to 15% of exact matches. Therefore, the linkage system uses probability matching by calculating the likelihood that a pair of records matches by comparing first initial, surname, sex, year, month and date of birth, and postcodes.

To ensure that the SMR data set are accurate, consistent, and comparable across time and between sources, the ISD monitors accuracy levels by undertaking routine quality assurance assessments, and the minimum target for accuracy is 90%. The Data Quality Assurance assessment of SMR01 inpatients and day cases were conducted in 2007 and 2012. The 2007 assessment examined records during 2004-2006; the report revealed that the accuracy of coding the main diagnosis was 88% in both inpatient and day case SMR01 episodes; and the accuracy rate for coding of the main operation was 92% for inpatient episodes and 95% for day cases (Information Services Division (ISD) and NHS National Services Scotland, 2007). The following assessment in 2012 investigated SMR records during 2010-2011; the overall accuracy rate of coding the main condition across Scotland remained the same at 88% and increased by 1% for main operation coding. For alcohol condition coding, the assessment of SMR01 reported that the accuracy rate was 95.9% in 2007 and 92.9% in 2012 (Information Services Division (ISD) and NHS National Services Scotland, 2012).

3.6.3 SHeS -SMR/NRS linkage data set

During face-to-face interviews, SHeS respondents were asked to give consent for their name, address, and date of birth to be sent to the ISD of NHS Scotland. This allowed for their Health Survey responses to be linked with the SMR data, i.e. medical diagnoses, in-patient and out-patient hospital visits, cancer registration, GP registration, and death records obtained from the NRS. Where consent is not given, the linkage does not take place. Then, the electronic Data Research and Innovation Service (eDRIS) links the consented SHeS participant data set to the SMR/NRS records via personal identifiers using established probability matching techniques (Information Services Division). This study used the SHeS-SMR/NRS linkage data for the 1995, 1998, 2003, 2008-2012 SHeS data sets, particularly SMR01 - which is the national data schemes that records comprehensive information including inpatient/day case activity, procedures and diagnoses, day surgery and outpatient procedures, multiple and all emergency admissions, and unintentional injuries admitted to National Health Service (NHS) hospitals in Scotland - and mortality, and follow-up from 1981 to the end of 2013 as shown in Figure 3-4. The selected covariates related to the baseline characteristics of the study cohort were derived from eight survey years of the SHeS; they included the age at survey date, gender, SIMD, alcohol consumption including the AUDIT score and binge drinking, smoking status (i.e. the number of cigarettes per day), self-reported health condition (i.e. having CVD and diabetes), physical activity, and BMI. In addition, prior non-alcohol related hospitalisation was examined to be a SHeS cohort baseline characteristic so the SMR records before the interview date of SHeS respondents who consented were used to define prior non-alcohol related hospitalisation. Finally, the SMR records were also used for identifying hospitalisation after the interview date, and NRS mortality records were defined as death of consenting SHeS participants.

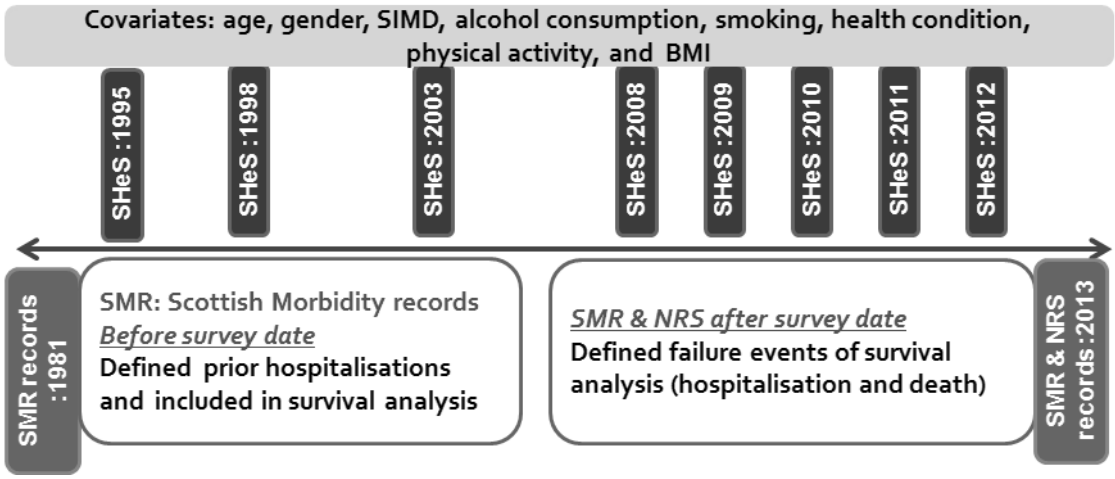


Figure 3-4 Scottish Health Survey (SHeS)/Scottish Morbidity Records (SMR) linkage data set

3.6.4 Dealing with missing data of SHeS -SMR/NRS linkage data

A comparison of survey estimates of population-level alcohol consumption with per-capita figures derived from data on national alcohol sales reveals a coverage gap of 30%-45% in Scotland (Hinchliffe, 2013, HM Revenue and Customs, 2012, Robinson et al., 2013). The under-reporting alcohol consumption in population surveys could be explained via drinking by people outside the sampling frame and non-responders to the survey, in particular, individuals with more problematic alcohol consumption patterns are typically underrepresented in health survey (Makela and Huhtanen, 2010, Kelfve and Ahacic, 2015, Meier et al., 2013, Gorman et al., 2014, Maclennan et al., 2012, Meiklejohn et al., 2012). For the SHeS, a lower response rate of individuals was found in males compared to females (Gray et al., 2013). The SHeS-SMR/NRS linkage data for the 1995, 1998, 2003, 2008-2010 reported lower rates of alcohol-related harm and all-cause mortality compared with population counterparts in a series of health surveys in Scotland, and greater non-response bias was associated with increased deprivation (Gorman et al., 2014). This study considered the nature of missingness (i.e. whether the data are missing or not) with reference to the classification of missing data mechanisms, i.e. data can be missing at random (MAR) or missing not at random (MNAR) (Rubin, 1987,

Gorman et al., 2017). MAR is the case where the probability of missingness is unrelated to the unobserved data taking the observed data into account. Alternatively, if the missingness depends upon unobserved data (even after all the information in the observed data are taken into account), the observations are MNAR. Note that data which are MNAR can become MAR if additional variables are observed and used in the analysis.

To apply this method to this study - which investigates alcohol-related hospitalisations and deaths among SHeS-SMR/NRS linkage data - Missing data are definitely not missing completely at random (MCAR) because the missingness was associated with measured variables. MNAR is still a possibility, but it was not considered due to the limitation of additional external information. Then, in this study MAR was assumed to impute missing data.

Following Gray et.al., an imputation techniques, namely multiple imputation (MI), is considered to be superior as it makes reliable estimation of variances and CIs relatively easy (Gray et al., 2013, Rubin, 1987). MI with chained equation is a scientifically robust way of dealing with missing data if MAR or MCAR holds (Clark and Altman, 2003). MI approach using chained equations was employed to fill missing data (Little and Rubin, 2002, Royston and White, 2011). The information in the observed values of hospitalisation and death records of the SHeS-SMR/NRS linkage data were used to predict the missing values i.e. age at survey date, alcohol drinking status at survey date with adjusted under-reporting alcohol consumption - the AUDIT score (0-40) and binge drinking (Y/N), number of cigarettes per day, CVD condition (Y/N), diabetes (Y/N), general health condition (3 groups of GHQ score), physical activity (no activity/low activity/medium activity/high activity), BMI (underweight/normal or BMI < 25, overweight or BMI 25 ≤ BMI < 30, obesity or BMI ≥ 30), prior non-alcohol related hospitalisation, and SIMD quintile (Office of the Chief Statistician, 2004). Once all missing values were multiply-imputed, the datasets were then analysed using standard techniques for complete data and combined using standard rules.

3.7 Ethical Issues

As this study uses secondary data, those who initiated the SHeS previously dealt with the ethical aspects of the survey (Dong and Erens, 1997, Shaw et al., 2000, Bromley et al., 2005, Bromley et al., 2009, Bromley et al., 2010, Bromley and Given, 2011, Bromley et al., 2012, Rutherford et al., 2013b). The study protocol was circulated to a Multi-Centre Research Ethics Committee in Scotland who approved the ethical aspects of the survey. During the survey period, all respondents were informed about scope of the SHeS (i.e. the study objectives, the use of survey data, and confidentiality) and then signed informed consent forms before the interview was undertaken.

Moreover, SHeS participants were asked to sign another consent form indicating whether they wished to consent for linking their SMR records with the interview data. The form explained that the research would be more useful as an eligible researcher would be able to determine how people's lifestyles and circumstances can have an impact on future health and use of hospital services; it also stated that the information would be confidential and used for research purposes only. Therefore, by signing the form, participants were only giving permission for the linking of this information to routine administrative data and nothing else.

In terms of information governance, this study protocol was approved by the NHS National Services Scotland Privacy Advisory Committee for accessing the NSS-NRS data set through the national data security system or Safe Haven provided by eDRIS (Information Services Division). The researchers who were granted access to this individual patient data have undergone appropriate training which is necessary to gain the 'approved researcher' status (Appendix 3).

Chapter 4: Predicting Alcohol Use Disorder Identification Test (AUDIT) score using Scottish Health Surveys

4.1 Introduction

This study investigates alcohol-related hospitalisations and deaths among alcohol drinkers in the Scottish Health Surveys (SHeS) participants, particular those with alcohol use disorders including harmful use, hazardous use, and probable alcohol dependence. To assess alcohol use disorder, the Alcohol Use Disorder Identification Test (AUDIT) is widely considered to be the screening tool used for detecting problematic alcohol use. It was developed to identify alcohol problem drinkers in terms of alcohol use disorders by the WHO's ICD-10 definition (World Health Organization, 1993). The AUDIT has been translated into many languages and is recommended for use in the primary healthcare setting for alcohol use disorders screening and treatment in the UK (National Collaborating Centre for Mental Health, 2011) as well as many other countries (Dybek et al., 2006, Gache et al., 2005, Babor et al., 2001, Pradhan et al., 2012, Kawada et al., 2011, Li et al., 2011, Areesantichai et al., 2010, Assanangkornchai et al., 2010).

Moreover, the use of the AUDIT in general population surveys was introduced to identify alcohol misuse in non-clinical samples which might be used in the policy context rather than the clinical context (Aalto et al., 2009, Dawson et al., 2005, Lundin et al., 2015, Rumpf et al., 2002). The SHeS 2012 implemented the AUDIT for estimating the prevalence of alcohol use disorders among survey participants; nevertheless, it was not used in the 1995-2011 waves of the SHeS (Dong and Erens, 1997, Shaw et al., 2000, Bromley et al., 2005, Bromley et al., 2009, Bromley et al., 2010, Bromley and Given, 2011, Bromley et al., 2012). To conduct further analyses, predicting the AUDIT scores for 1995-2011 would require modelling based on the SHeS 2012 data set as the

AUDIT was first measured in that year (Rutherford et al., 2013b). This chapter describes the approach used for the development of the prediction AUDIT score model to generate the predicted AUDIT scores for the SHeS in 1995, 1998, 2003, and 2008-2011.

4.2 Methods

4.2.1 Data sources

The SHeS from 1995, 1998, 2003, and 2008-2012 were analysed, using the SHeS 2012 to develop a fitted prediction model for predicting the AUDIT scores in all other waves (as described in Chapter 3 section 3.7.1). The SHeS 2012 on alcohol consumption among adults consisted of weekly units of alcohol consumption, unit consumption on the heaviest drinking day within the last week, problem drinking using the AUDIT, and social context of drinking (where respondents usually are when they drink and who they usually drink with) (Catto, 2008). The study population were adults aged group 16 years old and over since the collected information needed for the prediction model development was available, e.g. weekly unit alcohol consumption, unit consumption on the heaviest drinking day, and other related risk factors.

4.2.2 Modelling method

Alternative approaches were employed as demonstrated in Table 4-2, and these approaches were evaluated based on their predictive ability. From the SHeS 2012 data set, the AUDIT score distribution is presented in Figure 4-1. The AUDIT scores ranged from 0 to 36 (mean 3.98), and the distribution showed positive skewness with a large number of zeros (non-drinker) at approximately 26% of respondents and a very small number of high scores. These baseline figures can be used to guide the candidate models for predicting AUDIT scores.

Firstly, an ordinary least squares (OLS) regression was considered as it is the most common model used for continuous outcome under the normal

distribution assumption. OLS has shown to be a very robust method, especially with large data sets (Lumley et al., 2002). Although transformation is used to improve linearity and homogeneity of variance so that a standard linear model can be applied, the transformation has some drawbacks: 1) the response variable has changed, and has back-transformation problems; 2) the transformation must simultaneously improve the linearity and homogeneity of variance; and 3) the transformation does not overcome the protocol of point probability mass at the zero value.

Moreover, an alternative to transformation is the use of the generalised linear model (GLM) framework, of which OLS is equivalent to the GLM Gaussian families with identity function (McCullagh and Nelder, 1989, Dobson and Barnett, 2008). Hence, the GLM approach was the second candidate model, and it represents a re-parameterisation of the model that retains the original scale (in this case, the AUDIT score) of the response variable, so it has minimal assumptions and eliminates the need to transform the data. Moreover, GLMs can accommodate skewness in the AUDIT score distribution. This study performed a comparison between the three GLM families, i.e. Gaussian, gamma, and negative binomial, and the log-link function was used for these families.

Thirdly, to address the problem generated by zero-AUDIT score observations or non-drinkers (approximately 26% of respondents), two-part models were combined (Jones, 2000): 1) a binary logistic regression to predict the probability of being non-drinker (AUDIT score=0) and drinker (AUDIT score ≥1), and 2) the following part of the model included only drinkers (AUDIT score ≥1) using OLS regression and GLMs to estimate the predicted AUDIT score in score range of 1-40. Then, the overall predicted AUDIT score was derived from both part models as shown in Table 4-2.

Finally, the AUDIT questionnaire required a respondent to complete the 10 questions which were categorized into five levels of problems (score of 0, 1, 2, 3, and 4) for question 1 to 8, and 3 levels of problems (score of 0, 2, and 4)

for questions 9 and 10 (as shown in Table 3-1). Thus, an ordinal logistic regression was performed as the fourth alternative approach where the analysis examined the probability of answering the score for each of the 10 questions. Then, the total predicted score would be calculated by the weighted score of all AUDIT items. All statistical analyses were performed using STATA program version 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

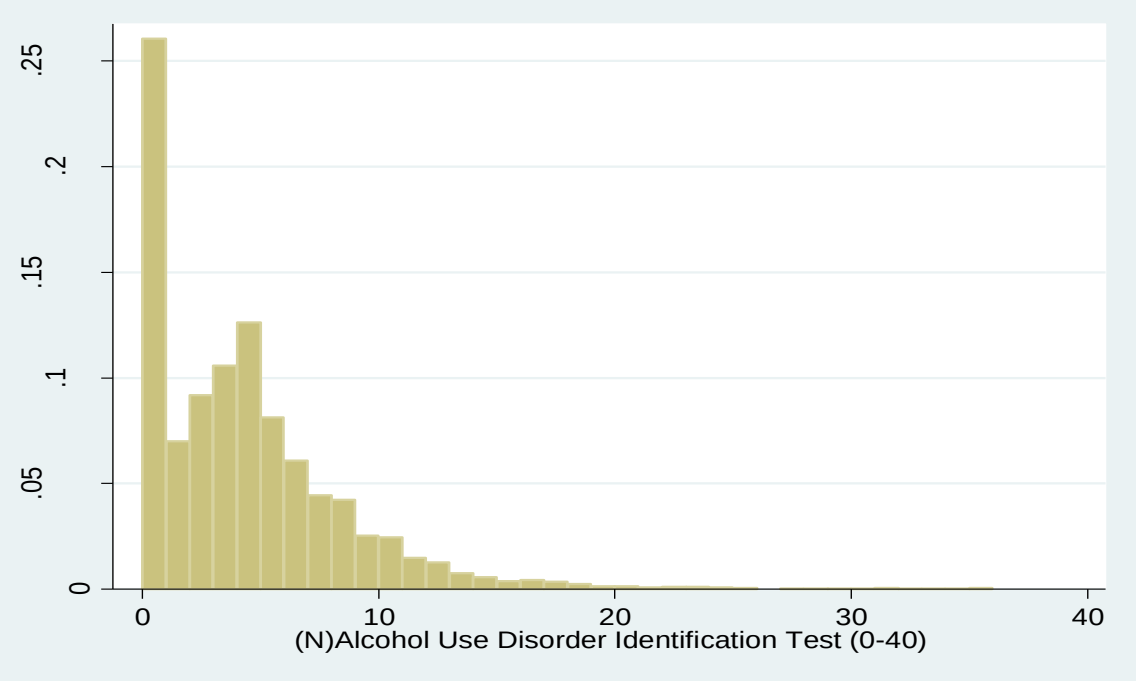


Figure 4-1 Distribution of AUDIT scores from the Scottish Health Surveys in 2012 (Skewness 2.14 Kurtosis 11.17)

4.2.3 Potential explanatory variables for AUDIT score modelling

The selection of explanatory variables particularly considered the variables which were measured in the SHeS during 1995-2011. Based on literature review, 15 variables which were found to be associated with alcohol drinking were considered in model selection process. These comprised age, marital status, parental status, weekly unit alcohol consumption (unit/week), unit drunk on heaviest day within last week (unit/day), smoking status

(Aekplakorn et al., 2008, De Leon et al., 2007, Falk et al., 2006, Harrison et al., 2008, McKee et al., 2010), general health condition (GHQ score), long-term condition (having cardiovascular condition), equivalised income, SIMD 2012 quintiles (Office of the Chief Statistician, 2004), NSSEC of household reference person (five groups professional), NSSEC of parental (five groups professional and selected highest level compared between parents), economic activity and highest educational qualification; these variables were analysed sub-grouped by gender.

Table 4-1 Candidate models for predicting the AUDIT score using the SHeS 2012 data set

Model	Method	Predicted AUDIT score $(\hat{A}_i)$ calculation
1	OLS regression	$\hat{A}_i = \hat{\alpha} + \sum_{j=1}^{k} \hat{\beta}_j X_{ij}$
2	GLM, Gaussian family, log-link function	$E(\hat{A}_i) = \hat{\mu}_i$
3	GLM, gamma family, log-link function	$g(\hat{\mu}_i) = \hat{\alpha} + \sum_{j=1}^{k} \hat{\beta}_j X_{ij}$
4	GLM, negative binomial family, log-link function	
5	2-part model: standard logistic regression & OLS regression	First part model: probability (π) of being drinker or AUDIT score ≥ 1 $\pi = \frac{\exp\{\alpha^{\pi} + \sum_{j=1}^{k} \beta_j^{\pi} X_{ij}\}}{1+\exp\{\alpha^{\pi} + \sum_{j=1}^{k} \beta_j^{\pi} X_{ij}\}}$ Second part model: predicting AUDIT score ≥ 1, A_i^{1+} $A_i^{1+} = \hat{\alpha} + \sum_{r=1}^{R} \hat{\beta}_j^{A1+} X_{ij}$
6	2-part model: standard logistic regression & GLM Gaussian family, log-link function	
7	2-part model: standard logistic regression & GLM Gamma family, log-link function	
8	2-part model: standard logistic regression & GLM, Negative binomial family, log-link function	$\hat{A}_i = \hat{\pi}\hat{A}_i^{1+} = \frac{\exp\{\hat{\alpha}^{\pi} + \sum_{r=1}^{R} \hat{\beta}_j^{\pi} X_{ij}\}}{1 + \exp\{\hat{\alpha}^{\pi} + \sum_{r=1}^{R} \hat{\beta}_j^{\pi} X_{ij}\}} \blacksquare \left[\hat{\alpha} + \sum_{r=1}^{R} \hat{\beta}_j^{A1+} X_{ij}\right]$
9	Ordered logistic regression for 10-item AUDIT questionnaire	The AUDIT score of each 10-question (A) was divided into c categories, where P(A ≤ c), c = 1, 2,… , k. $P(A_i \le c) = p_{i1} + \cdots + p_{ic}$ $P(A_i \le c) = \frac{\exp\{\alpha_i^{Pc} + \sum_{j=1}^{k} \beta_j^{Pc} X_{ij}\}}{1 + \exp\{\alpha_i^{Pc} + \sum_{j=1}^{k} \beta_j^{Pc} X_{ij}\}}$ The predicted scores of each question were calculated using weighted score by predicted probabilities

*AUDIT: Alcohol Used Disorders Identification Test; OLS: ordinary least square; GLM: generalised linear model; RMSE: root mean square error

4.2.4 Model selection and validation

All candidate prediction models of the AUDIT score were assessed based on their performance (predictive ability) for predicting AUDIT scores using split-sample validation (Steyerberg et al., 2009). The sample was divided into two groups where the prediction model was developed from the first part of the data (training set) and then the predicted values of the second part (test data set) were derived from the developed model. This study systematically split the SHeS 2012 data set into two groups via the given archive serial number of the individual; a typical split is 2/3:1/3 for training and test samples, respectively (Steyerberg et al., 2009, Picard and Berk, 1990). Then, the predicted AUDIT scores were derived from the test data set of each alternative model. This study adopted a validation criterion for alternative models from the previous cost prediction study (Lipscomb et al., 1998) using a squared-error loss function (corresponding to the root mean square error, or RMSE):

$$RMSE^j = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(A_i - \hat{A}_i^j)^2}$$

where A_i is the observed AUDIT score and $\hat{A}_i^j$ is the predicted score for j=1, .., 9 of models under evaluation. The RMSE of the candidate models was calculated to compare their performance in predicting the AUDIT score as the better fit models minimise the RMSE.

4.3 Results

4.3.1 Comparing predicted AUDIT scores of the alternative models

The results of the predicted value and predictive ability of each model are shown in Table 4-3. Compared to the observed values, the predicted AUDIT scores from almost all models showed out-of-range scores which were either a

negative value or greater than 40, range from 0.03% to 1.9% of predicted values. Thus, an additional analysis was conducted to adjust the predicted values so that they would be in range of the observed scores of 0 to 36; the given RMSEs of the adjusted value were also presented. From an unadjusted RMSE standpoint, the OLS regression model showed the best predictive ability for the AUDIT score (RMSE=2.74), although its predicted value showed a negative value (-0.045). Comparatively, the 2-part model of binary logistic regression combined with OLS regression also showed good predictive performance (RMSE=3.02), and there was no out-of-range predicted score, followed by the 2-part model GLM Gaussian family log-link function (RMSE=3.27), ordered logistic regression (RMSE=3.34), and GLM Gaussian family log-link function (RMSE=3.81). On the contrary, the models which show the worst predictive ability were the log-link function of GLM gamma (RMSE=794) and negative binomial (RMSE=223) families as well as the 2-part model for those (RMSE=12.55 for GLM gamma family and RMSE=10.18 for negative binomial family). Ultimately, after adjusting for out-of-range scores, the OLS regression model showed the best predictive performance (RMSE=2.73) even though the RMSE of all candidate predictions models was able to be minimised.

4.3.2 Subgroup analysis by gender of the AUDIT score prediction model

Additionally, a subgroup analysis by gender was performed for predicting AUDIT scores using gender-specific explanatory variables for all nine candidate models. After that, the overall RMSEs of males and females were also computed to compare between the observed AUDIT score and the combined predicted values from the various models. Table 4-4 shows the results of the predicted AUDIT score of the 9 candidate models. Comparing the RMSEs between the two analyses (the subgroup and without the subgroup) found that the subgroup analysis was able to slightly improve the predictive performance of all candidate models. OLS regression also achieved the best predictive performance model for subgroup analysis by gender where the RMSE decreased

to 2.68 and there were no out-of-range scores in males. For other alternative models, the rank of their predictive performance was similar to the order of the previous analysis with decreasing RMSEs. Thus, the OLS regression subgroup by gender was selected to carry out the prediction of AUDIT scores for the SHeS in 1995, 1998, 2003, and 2008-2011 due to its accuracy.

Table 4-2 Predictive ability of prediction model in the test data set (1/3)

	Model	AUDIT score				RMSE	% of prediction out of range	RMSE of adjusted prediction
		Mean	SE	Min	Max			
	Observed value	***3.938***	***0.110***	***0***	***36***			
1	OLS regression	3.979	0.098	-0.045	37.65	2.74	0.3%	2.729
2	GLM Gaussian, log-link	4.259	0.116	0.727	76.76	3.81	0.1%	3.140
3	GLM Gamma, log-link	36.873	23.351	0.559	24293	794	1.9%	4.427
4	GLM Negative binomial, log-link	13.753	6.575	0.686	6738	223	1.2%	4.028
5	2-part OLS regression	3.683	0.073	0.307	27.17	3.02	NA	NA
6	2-part GLM Gaussian, log-link	3.950	0.070	0.425	37.84	3.27	0.03%	3.259
7	2-part GLM Gamma, log-link	4.310	0.386	0.400	383	12.55	0.3%	3.312
8	2-part GLM Negative binomial, log-link	4.189	0.315	0.407	310	10.18	0.3%	3.258
9	Ordered logistic regression	3.950	0.125	0.338	40	3.34	0.3%	3.306

OLS: ordinary least square; GLM: generalized linear model; RMSE: root mean square error; NA: not applicable

Table 4-3 Predictive ability of prediction model in the test data set (1/3), subgroup males and females

Model		AUDIT score					
		Mean	SD	SE	Min	Max	RMSE
	Males	*4.89*	*4.64*	*0.19*	*0.00*	*36.00*	
	Females	*3.25*	*3.70*	*0.13*	*0.00*	*33.00*	
Model 1	**Males**	**4.94**	**3.74**	**0.17**	**0.06**	**34.25**	**2.680**
OLS regression	**Females**	**3.23**	**2.66**	**0.11**	**-0.15**	**21.64**	
Model 2	Males	5.24	4.15	0.19	1.26	56.53	3.366
GLM Gaussian, log link	Females	3.42	2.79	0.11	0.66	36.58	
Model 3	Males	21.71	261.89	11.92	0.76	5352.01	173.886
GLM Gamma, log link	Females	4.97	22.62	0.89	0.37	526.38	
Model 4	Males	12.23	109.45	4.98	0.94	2168.33	72.363
GLM Negative binomial, log link	Females	3.95	10.06	0.40	0.54	210.98	
Model 5	Males	4.54	2.57	0.12	0.38	19.87	2.995
2-part OLS regression	Females	2.96	2.09	0.08	0.26	19.64	
Model 6	Males	4.82	2.36	0.11	0.66	26.05	3.204
2-part GLM Gaussian, log link	Females	3.14	2.02	0.08	0.33	25.48	
Model 7	Males	5.06	8.46	0.38	0.65	165.37	5.660
2-part GLM Gamma, log link	Females	3.07	3.05	0.12	0.34	52.46	
Model 8	Males	4.98	7.29	0.33	0.65	140.48	4.998
2-part GLM Negative binomial, log link	Females	3.06	2.82	0.11	0.35	46.41	
Model 9	Males	4.85	4.63	0.21	0.47	38.87	3.304
Ordered logistic regression	Females	3.27	3.69	0.146	0.19	35.56	

OLS: ordinary least square; GLM: generalized linear model; RMSE: root mean square error

4.4 Discussion

This study explored the use of the AUDIT for detecting alcohol use disorder in general population surveys, i.e. SHeS from 1995-2012 for a total of eight surveys. The reason for this is because the AUDIT will also be employed in further analyses to investigate alcohol use-related morbidity and mortality of SHeS participants. This chapter describes the method used for developing the prediction of AUDIT scores since the AUDIT was not measured in the SHeS from 1995-2011 as it was only introduced in the SHeS 2012 onwards. The fitted prediction models of the AUDIT score were developed and evaluated using the SHeS 2012 data set. A comparison of alternative prediction models was demonstrated. Nine candidate models using a different standard linear framework, GLM framework and two-part models were compared for their predictive abilities. The main finding showed that the best predictive AUDIT model was the OLS regression model using subgroup analysis by gender.

The best-fitted model was able to generate the overall score, yet each AUDIT question could not be specifically predicted. This is an important concern because the main score comprises the total score from the 10 different questions with three main contents (i.e. hazardous use, harmful use and possible dependence). Having different scores for sub-questions compared to the observed values while still having the correct total score will definitely lead to inaccuracies and could result in improper analysis. Moreover, the OLS regression model might not be the perfect model to predict the AUDIT as shown by its RMSE of 2.68, meaning that the predicted AUDIT score could be over- or underestimated by approximately three units. Based on the cut-off for alcohol use disorder (Reinert and Allen, 2007), the three different scores might be clinically significant for moderate-risk drinkers as their predicted score might be erroneous because their drinking risk might be of a higher risk or lower risk.

Moreover, the observed AUDIT scores were derived from general population surveys, i.e. SHeS 2012. There are specific issues which were

addressed when using the AUDIT in the context of surveys, especially using overall scores for interpretation rather than each AUDIT item (Knibbe et al., 2006). Firstly, the interpretation of responses to the AUDIT items is more controlled in a healthcare setting than general population surveys so using the AUDIT in population surveys might lead to the possibility of a false positive in the total score (Kypri et al., 2002). Secondly, compared with the population in a healthcare setting, the general population are likely to be much more heterogeneous in their drinking patterns and the related consequences due to alcohol consumption. Moreover, under-reporting bias of alcohol consumption has been frequently raised as an important issue in alcohol consumption surveys (Babor et al., 2010a, Meier et al., 2013, Boniface and Shelton, 2013).

4.5 Conclusions

This study focuses on alcohol use disorders identified by the AUDIT in general population surveys, so a model to predict AUDIT scores for the study population of the SHeS surveys from 1995, 1998, 2003, and 2008-2011 was generated to allow for further analyses. This analysis thoroughly developed statistical approaches to select the best predictive performance model of predicting AUDIT scores among all plausible candidate models. Although the selected AUDIT score prediction model (i.e. the OLS regression separated model by gender) could properly predict the scores, these scores for most of the SHeS study samples (7 of 8 surveys) is still an important assumption that will be used for estimating predicted life expectancy, quality-adjusted life year, and lifetime cost. The limitations of the interpretation of the relationship between the predicted AUDIT score and outcomes of interest should be noted, and this has been raised in this chapter.

Chapter 5: Estimation of the health-related quality of life among alcohol use

5.1 Introduction

Recently, researchers have shown an increased interest on economic evaluations of alcohol consumption control programmes to assess their effectiveness to inform policy makers (Anderson et al., 2009a, Watson et al., 2013, Doran et al., 2010, Barbosa et al., 2010b, UKATT Research Team, 2005b). A generic health outcome of quality-adjusted life years (QALY) is recommended as an estimation measure of effectiveness among health interventions in health technology assessment guidelines in the UK and many other countries (ISPOR, 2014, NICE, 2013). QALY captures two main aspects: the quantity (time the patient spent alive) and health-related quality of life (HRQoL) in term of utility (the component of QoL that health and health care can influence). To quantify the health utility score, different domains related to HRQoL are combined and converted them into a single preference-based HRQoL score. In general, the utility score varies from 0 (death) to 1 (full health). It is also possible to have states regarded as worse than death, which are represented by a negative value (NICE, 2013, Thavorncharoensap, 2014).

The commonly-used outcome measurements for alcohol consumption control programmes are alcohol consumption levels, episodic drinking, and assessment of alcohol drinking problems, e.g. the AUDIT (NICE, 2011, Watson et al., 2013, Babor et al., 2001). Moreover, HRQoL measured by utility score is becoming increasingly important in terms of an outcome measurement for cost-utility analyses of alcohol interventions which aim to reduce alcohol-related harm and improve HRQoL of alcohol use disorders, especially in alcohol-dependent patients (Donovan et al., 2005, Essex et al., 2014, Gunther et al., 2008). The measured outcome can not only be used to compare the effectiveness between alcohol interventions, but can also apply the utility index as a single unit outcome measurement in the health policy context, so

that comparisons across health interventions for different target populations can be made for policy decision-making. As discussed in Chapter 4, differences were found in consequences associated with alcohol use between the population in the clinical setting and survey population, including the assumption about alcohol use disorder severity. It can be implied that HRQoL related to alcohol use disorder between the two groups would also be different as well as the outcome evaluation of the alcohol intervention provided in the clinical setting and population level. However, the current study focuses solely on the outcome measurement in the general population.

Four previous studies used a cross-sectional design and examined the association between different alcohol consumption levels and HRQoL in the general population survey (Petrie et al., 2008, Saarni et al., 2008, Valencia-Martin et al., 2013, Van Dijk et al., 2004). Preference-based HRQoL instruments as EQ-5D and Medical Outcomes Study Short Forms (i.e. SF-6D, SF-12 and SF-36) were used to calculate HRQoL as health utility index. The initial results of studies on the relationship between alcohol consumption patterns and HRQoL from multiple countries have been inconsistent. A major challenge in such research is the use of different methods of categorising alcohol consumption patterns (e.g. the AUDIT, Quantity-Frequency-Variability methods, Weekly drinking Recall, or binge drinking episodes), which creates difficulty in comparing study results, and possibly produces differing results regarding the potential positive effects of moderate alcohol consumption on HRQoL. The initial findings were that HRQoL was slightly worse than low- and moderate-risk drinkers after adjusting for confounders of abstainers (never drinkers) and former drinkers, and only high-risk drinkers reported the worst HRQoL.

A cost-utility analysis of alcohol interventions will be carried out to determine the health benefits from reducing alcohol use or alcohol-related harms, e.g. QALY gained. Thus, this study aims to estimate the health consequences of different alcohol use classified by AUDIT measurements; this chapter will focus on HRQoL in terms of utility values. The main issue addressed in this chapter is the estimation of HRQoL among different AUDIT scores. The results will subsequently be used for QALY calculations in further analyses.

5.2 Methods

5.2.1 Study sample

The SF-12 from the SHeS 2003 was measured among respondents aged 18 and over (Gray and Leyland, 2005). The SF-12 is a widely used self-reported generic measure of health status, yielding both physical component (PCS) and mental health component (MCS) summary scale scores (Ware et al., 2001). All eligible respondents were asked about eight concepts comprising aspects of their general health, physical functioning, limitations to normal activities due to physical health problems or emotional problems, bodily pain, vitality (energy/fatigue), social functioning, and mental health (psychological distress and psychological well-being) as shown in Appendix 4.

5.2.2 Data analysis

Utility estimation

Although SF-12 measures HRQoL, it cannot be used for calculating QALY as it requires a preference-based single index measure of health. As such, Brazier and Roberts (2004) developed an estimation of a preference-based measure of health from SF-12. Firstly, the number of dimensions was reduced from 12 to 6 - namely SF-6D (SF-12) - by including physical functioning, social functioning, pain, mental health, and vitality, combining the limitations (physical and emotional) into a single dimension, and excluding the general health item. From then, seven of the SF-12 items were assigned to the six dimensions of SF-6D (SF-12) as shown in Appendix 5. Lastly, the estimation of preference-based values for each health state was calculated using coefficients of the developed model as shown in Table 5-1 (Brazier and Roberts, 2004).

For example, the shortened SF-12 to SF-6D of a SHeS respondent is reported as follows: Physical functioning [PF2]=2 (a little limitation in moderate activities), Role limitations [RL4]=4 (limitations of physical health and having

emotional problems, 'most severe'), Social functioning [SF3]=3 (limitation of social activities some of the time), Pain [PAIN2]=2 (a little bit of pain), Mental health [MH3]=3 (feeling downhearted and low some of the time), and Vitality [VIT4]=4 (having a lot of energy not very often). Then, the total SF-6D (SF-12) score is calculated using the equation below:

SF-6D (SF-12) score = 1- 0[PF2] - 0.063[RL4] - 0.066[SF3] - 0[PAIN2] - 0.059[MH3] - 0.078[VIT4] - 0.077[MOST SEVERE]

$$= 0.657$$

The overall SF-6D (SF-12) scores of SHeS participants were presented as the average score classified by age groups, gender, and SIMD to represent the baseline utility values of a normal population.

Table 5-1 SF-6D (SF-12) model for valuing health state index
(Brazier and Roberts, 2004)

Dimension	Coefficient
Constant (full health)	1.000
Physical functioning	
3*	-0.045
Role limitations (physical and emotional health)	
2	-0.063
3*	-0.063
4*	-0.063
Social functioning	
2	-0.063
3	-0.066
4*	-0.081
5*	-0.093
Pain	
3	-0.042
4*	-0.077
5*	-0.137
Mental health	
2	-0.059
3	-0.059
4*	-0.113
5*	-0.134
Vitality	
2	-0.078
3	-0.078
4	-0.078
5*	-0.106
Most severe*	
	-0.077

*When 1 or more dimension of health state is at the "most severe" level, an additional effect is taken into account with a value of -0.077.

Multivariate analysis

A multiple linear regression was conducted to examine the relationship between alcohol use in terms of the AUDIT score and HRQoL; however, the AUDIT was not measured in the SHeS 2003. The prediction model developed in Chapter 4 was employed for predicting the AUDIT scores of the SHeS 2003 data set using 15 covariates, i.e. age, gender, marital status, parental status, weekly unit alcohol consumption (units/week), units consumed on the heaviest day (units/day), smoking status, general health condition (GHQ score), long-term condition (having cardiovascular condition), equivalised income, SIMD, NSSEC of household reference person (five groups professional), NSSEC of parental (five groups professional and selected highest level compared between parents), economic activity, and highest educational qualification. The predicted AUDIT scores at survey date range from 0-40, where 0 defines a current non-drinker – including those who are former drinkers and those who have never consumed alcohol.

Moreover, other covariates which were measured in the SHeS and have been found to have an independent relationship with HRQoL were included in the multiple linear regression of the SF-6D (SF-12) index (Gray and Leyland, 2005); these are age at survey date and SIMD (Office of the Chief Statistician, 2004). To estimate the impact of alcohol-related and non-alcohol related hospitalisation on HRQoL in terms of utility decrement, prior hospitalisation was also included in the multivariate analysis compared to no prior hospitalisation (reference group) and was classified into four groups: 1) prior wholly alcohol-related hospitalisation; 2) prior partly alcohol-related hospitalisation; 3) prior CVD hospitalisation; and 4) prior non-CVD hospitalisation using the ICD-9 and ICD-10 of primary diagnosis (Appendix 1). Only the most recent hospitalisation was used to determine an individual participant's group. Moreover, the period of each hospitalisation was also categorised to be either within the last year or more than one year ago. To define each hospitalisation before the interview date, the linkage data between

the SHeS 2003 and the NHS National Services Scotland (NSS) data sets was explored (see more details in Chapter 3:) using the ICD-9 and ICD-10 list to classify prior hospitalisation of SHeS participants (Jones and Bellis, 2014, Jones et al., 2008, Grant et al., 2009). The NHS-NSS data set used in the analysis included the Scottish Morbidity Record (SMR) 01 (inpatients and day cases). All statistical analyses were performed using STATA program version 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP). A two-side test with a ρ-value of less than 0.05 was considered statistically significant.

Dealing with missing data

A multiple imputation approach using chained equations was undertaken to replace missing data (Little and Rubin, 2002, Royston and White, 2011). The information in the observed values of the covariates was used to predict the missing values. To apply this method to the study, missing at random (MAR) was assumed to impute missing data based on all predictors used in the multivariate analysis. Once 100 imputation data sets are created and analysed, the results are combined using standard rules (Rubin, 1987).

5.3 Results

SF-6D (SF-12) HRQoL scores of the SHeS 2003 respondents are shown in Table 5-2. These results revealed differences in HRQoL classified by gender due to age, alcohol drinking status (classified by the grouped AUDIT score), SIMD, and prior alcohol-related and non-alcohol related hospitalisations. The predicted AUDIT score ranges from 0-40 and are categorised into four groups as follows: 1) Low risk drinker: predicted AUDIT score=1-7 for males and 1-5 for females; 2) Hazardous drinker: predicted AUDIT score=8-15 for males and 6-12 for females; 3) Harmful drinker: predicted AUDIT score=16-19 for males and 13-16 for females; and 4) Probable dependence: predicted AUDIT score>=20 for males and >=17 for females (Reinert and Allen, 2007, Gache et al., 2005, Aalto

et al., 2009, Neumann et al., 2004, Dybek et al., 2006). The results showed that current non-drinkers, i.e. those who are former drinkers or have never consumed alcohol before, reported worse HRQoL scores than low-risk drinkers, while high-risk drinkers - who are categorised to be probable alcohol dependent patients in terms of the AUDIT - showed the worst HRQoL compared to other groups.

Figure 5-1 presents the observed mean and 95% CI of SF-6D (SF-12) score of HRQoL across each unit of predicted AUDIT score (0 to 15 and over). In both males and females, the higher AUDIT scores demonstrated a slight decrease of HRQoL with different magnitudes specific to the gender. To estimate the QALYs of different subgroups for further analyses which will use the alcohol intervention model that was developed in Chapter 3, the baseline HRQoL scores of the general population were also estimated and classified by gender, aged groups, and SIMD as shown in Table 5-3 for males and Table 5-4 for females. Compared to the baseline HRQoL scores, it is shown that a decreasing score is correlated with an increase in age and higher deprivation (shown as lower SIMD quintile) in both males and females.

Furthermore, the results obtained from the multiple linear regression using the multiple imputation approach of SF-6D (SF-12) HRQoL score classified by gender are presented in Table 5-5. For females, in all cases apart from wholly alcohol-related hospitalisation, HRQoL was more affected for those who were hospitalised within the last year compared to if they had undergone hospitalisation further back. For males, wholly alcohol-related hospitalisation impacted HRQoL more than partly alcohol-related hospitalisation but this was not seen for females. Moreover, prior alcohol-related hospitalisation had a similar impact on HRQoL as prior CVD hospitalisation, demonstrating the severity of impact of alcohol-related consequence. The AUDIT score had a stronger association with HRQoL for males than it did for females. For both males and females, the SIMD had a dose-response type of association with HRQoL where the more deprived SIMD correlated to a statistically significant

decrease in the SF-6D (SF-12) HRQoL score. The means of the R-square values derived from the imputations were 0.089 (min-max: 0.077-0.109) for males and 0.125 (min-max: 0.107-0.153) for females.

To investigate the impact of hospitalisation on current HRQoL, the scores were compared between those who had no hospitalisation before the survey date and those who had any alcohol-related and non-alcohol related hospitalisations within last year and over one year. For males, the reduction of HRQoL score due to hospitalisation ranged from 0.072 (SE=0.021, p=0.001) to 0.123 (SE=0.046, p=0.008) for wholly alcohol-related condition, 0.027 (SE=0.008, p=0.001) to 0.069 (SE=0.026, p=0.008) for partly alcohol-related condition, was 0.043 (SE=0.001, p<0.001) for non-alcohol related and non-CVD condition, and ranged from 0.078 (SE=0.009, p<0.001) to 0.134 (SE=0.022, p<0.001) for non-alcohol related with CVD condition.

For females, the impact of prior hospitalisation on current HRQoL are presented as the decrement HRQoL score due to different conditions. There scores were 0.08 (SE=0.021, p<0.001) for wholly alcohol-related condition, range from 0.043 (SE=0.006, p<0.001) to 0.126 (SE=0.024, p<0.001) for partly alcohol-related condition, between 0.017 (SE=0.005, p<0.001) and 0.048 (SE=0.007, p<0.001) for non-alcohol related and non-CVD condition, and a range from 0.097 (SE=0.01, p<0.001) to 0.109 (SE=0.026, p<0.001) for non-alcohol related with CVD condition.

Table 5-2 SF-6D (SF-12) score of HRQoL of the SHeS 2003 participants aged 18 years and over, classified by gender

	SF-6D (SF-12) HRQoL score					
	Males			Females		
	N	Mean	SD	N	Mean	SD
Age at survey date (years)						
18-24	131	0.83	0.101	193	0.815	0.111
25-34	393	0.823	0.119	529	0.811	0.115
35-44	639	0.821	0.127	781	0.806	0.126
45-54	529	0.809	0.139	703	0.787	0.134
55-64	540	0.802	0.148	651	0.79	0.142
65-74	423	0.788	0.15	450	0.776	0.15
>=75	240	0.778	0.146	357	0.728	0.165
Alcohol drinking status*						
Never drinker	94	0.823	0.145	268	0.752	0.163
Former drinker	129	0.726	0.182	184	0.705	0.163
Low risk drinker	1413	0.823	0.126	1332	0.811	0.121
Hazardous drinker	322	0.803	0.123	431	0.800	0.122
Harmful drinker	18	0.749	0.162	9	0.751	0.143
Probable dependence	13	0.668	0.151	9	0.743	0.148
Prior wholly AR hospitalisation						
No prior hospitalisation	2847	0.809	0.136	3626	0.79	0.137
last year	8	0.606	0.163	1	0.922	-
over 1 year	40	0.712	0.166	37	0.693	0.158
Prior partly AR hospitalisation						
No prior hospitalisation	2579	0.810	0.135	3153	0.797	0.134
last year	21	0.717	0.163	29	0.631	0.151
over 1 year	295	0.786	0.149	482	0.752	0.149
Prior non-CVD hospitalisation						
No prior hospitalisation	1359	0.810	0.139	1517	0.799	0.132
last year	231	0.749	0.16	351	0.738	0.156
over 1 year	1305	0.815	0.128	1796	0.791	0.136
Prior CVD hospitalisation						
No prior hospitalisation	2608	0.815	0.13	3425	0.795	0.134
last year	35	0.677	0.175	25	0.686	0.166
over 1 year	252	0.738	0.167	214	0.706	0.162
Scottish Index of Multiple Deprivation (SIMD)						
5th (Least deprived)	545	0.831	0.118	672	0.833	0.109
4th	651	0.83	0.118	825	0.808	0.122
3rd	689	0.81	0.136	830	0.791	0.137
2nd	531	0.796	0.146	692	0.771	0.145
1st (Most deprived)	465	0.759	0.157	634	0.739	0.156

*Low risk drinker: predicted AUDIT score=1-7 for males and 1-5 for females; Hazardous drinker: predicted AUDIT score=8-15 for males and 6-12 for females; Harmful drinker: predicted AUDIT score=16-19 for males and 13-16 for females; and Probable dependence: predicted AUDIT score>=20 for males and >=17 for females; AUDIT: Alcohol Use Disorders Identification Test

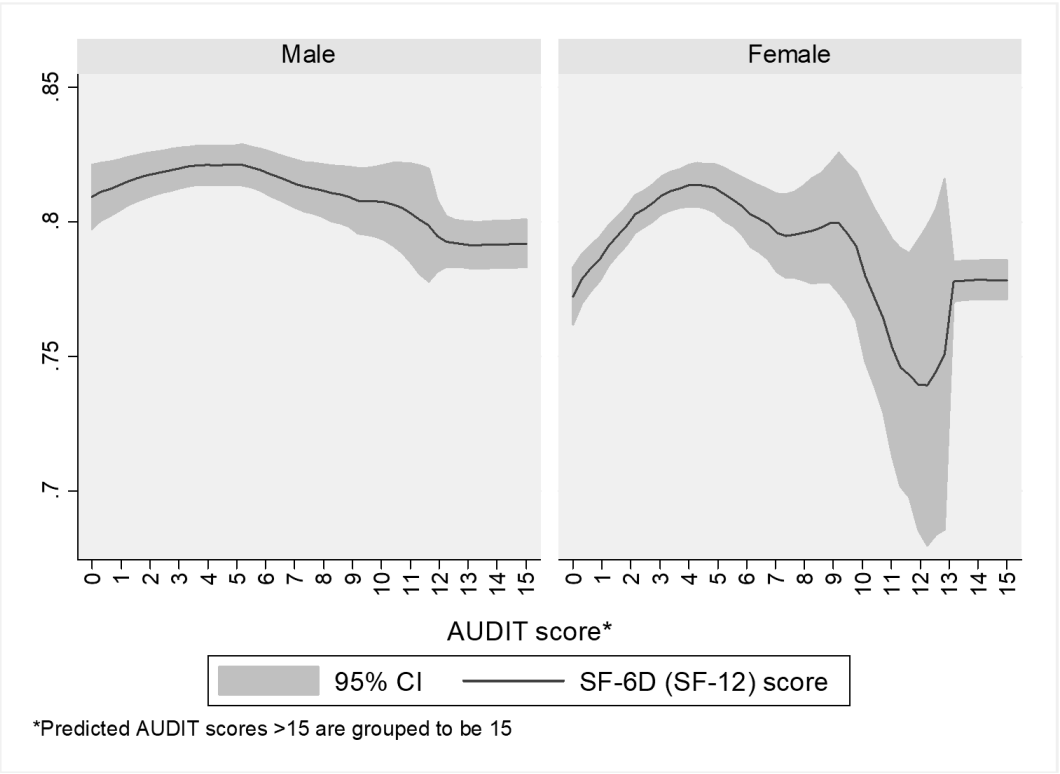


Figure 5-1 Observed mean and 95% CI of SF-6D (SF-12) HRQoL score across the predicted AUDIT score (0 to 15 and greater than 15) among SHeS 2003 participant aged 18 years and over, classified by gender

Table 5-3 Baseline SF-6D (SF-12) HRQoL scores of SHeS 2003 participants across SIMD quintile: males

Aged group (years)	Scottish Index of Multiple Deprivation (SIMD)				
	5th (least deprived)	4th	3rd	2nd	1st (most deprived)
All (N)	(634)	(701)	(691)	(597)	(482)
Mean	0.831	0.826	0.81	0.795	0.754
95% CI	*(0.808, 0.854)*	*(0.803, 0.849)*	*(0.785, 0.836)*	*(0.766, 0.825)*	*(0.719, 0.79)*
18-24 (N)	(23)	(27)	(27)	(32)	(31)
Mean	0.822	0.853	0.834	0.857	0.787
95% CI	*(0.787, 0.857)*	*(0.824, 0.881)*	*(0.795, 0.873)*	*(0.828, 0.887)*	*(0.745, 0.83)*
25-34 (N)	(75)	(88)	(88)	(104)	(70)
Mean	0.848	0.849	0.823	0.816	0.774
95% CI	*(0.826, 0.871)*	*(0.83, 0.867)*	*(0.796, 0.85)*	*(0.794, 0.839)*	*(0.741, 0.807)*
35-44	(146)	(164)	(155)	(125)	(97)
Mean	0.834	0.838	0.823	0.811	0.777
95% CI	*(0.816, 0.852)*	*(0.82, 0.855)*	*(0.805, 0.841)*	*(0.787, 0.835)*	*(0.744, 0.81)*
45-54	(128)	(139)	(126)	(82)	(96)
Mean	0.825	0.827	0.808	0.791	0.762
95% CI	*(0.805, 0.845)*	*(0.806, 0.849)*	*(0.783, 0.833)*	*(0.756, 0.826)*	*(0.729, 0.794)*
55-64	(138)	(127)	(121)	(111)	(80)
Mean	0.845	0.803	0.82	0.782	0.718
95% CI	*(0.826, 0.865)*	*(0.78, 0.826)*	*(0.796, 0.843)*	*(0.751, 0.813)*	*(0.68, 0.757)*
65-74	(86)	(89)	(107)	(92)	(72)
Mean	0.813	0.822	0.802	0.761	0.732
95% CI	*(0.784, 0.841)*	*(0.791, 0.853)*	*(0.775, 0.83)*	*(0.729, 0.792)*	*(0.697, 0.768)*
> 74	(38)	(67)	(67)	(51)	(36)
Mean	0.797	0.802	0.756	0.775	0.732
95% CI	*(0.75, 0.843)*	*(0.77, 0.835)*	*(0.722, 0.791)*	*(0.731, 0.818)*	*(0.685, 0.779)*

Table 5-4 Baseline SF-6D (SF-12) HRQoL scores of SHeS 2003 participants across SIMD quintile: females

Aged group (years)	Scottish Index of Multiple Deprivation (SIMD)				
	5th (least deprived)	4th	3rd	2nd	1st (most deprived)
All (N)	(784)	(873)	(858)	(749)	(685)
Mean	0.826	0.807	0.785	0.769	0.737
95% CI	(0.806, 0.846)	(0.786, 0.828)	(0.761, 0.809)	(0.743, 0.795)	(0.707, 0.766)
18-24 (N)	(30)	(37)	(36)	(48)	(59)
Mean	0.846	0.81	0.78	0.799	0.816
95% CI	(0.813, 0.88)	(0.779, 0.842)	(0.739, 0.821)	(0.765, 0.832)	(0.787, 0.845)
25-34 (N)	(105)	(122)	(114)	(128)	(104)
Mean	0.839	0.816	0.822	0.803	0.775
95% CI	(0.822, 0.856)	(0.795, 0.836)	(0.803, 0.841)	(0.78, 0.825)	(0.749, 0.8)
35-44 (N)	(176)	(198)	(172)	(150)	(142)
Mean	0.837	0.827	0.794	0.788	0.748
95% CI	(0.823, 0.852)	(0.812, 0.841)	(0.773, 0.815)	(0.769, 0.808)	(0.722, 0.774)
45-54 (N)	(180)	(166)	(157)	(128)	(117)
Mean	0.827	0.793	0.78	0.769	0.736
95% CI	(0.812, 0.843)	(0.773, 0.812)	(0.758, 0.802)	(0.745, 0.792)	(0.708, 0.764)
55-64 (N)	(133)	(162)	(167)	(126)	(105)
Mean	0.835	0.815	0.791	0.769	0.701
95% CI	(0.816, 0.854)	(0.798, 0.832)	(0.768, 0.814)	(0.742, 0.796)	(0.67, 0.732)
65-74 (N)	(96)	(102)	(118)	(86)	(87)
Mean	0.827	0.803	0.792	0.742	0.702
95% CI	(0.803, 0.851)	(0.776, 0.83)	(0.766, 0.818)	(0.709, 0.776)	(0.668, 0.736)
> 74 (N)	(64)	(86)	(94)	(83)	(71)
Mean	0.741	0.765	0.715	0.693	0.689
95% CI	(0.702, 0.779)	(0.732, 0.798)	(0.681, 0.748)	(0.655, 0.731)	(0.652, 0.726)

Table 5-5 Multiple linear regression using multiple imputation approach of SF-6D (SF-12) HRQoL score of SHeS 2003 participants aged 18 years and over, classified by gender

	Males					Females				
Covariate*	**Coefficient**	**SE**	***p-value***	**95%CI**		**Coefficient**	**SE**	***p-value***	**95%CI**	
Age at survey date	-0.001	0.0002	<0.001	-0.001	0.000	-0.001	0.0002	<0.001	-0.001	-0.001
Predicted AUDIT score	-0.004	0.001	<0.001	-0.006	-0.002	-0.002	0.001	0.030	-0.005	-0.0002
Prior wholly alcohol-related hospitalisation										
last year	-0.123	0.046	0.008	-0.212	-0.033	0.031	0.099	0.755	-0.163	0.225
over 1 year	-0.072	0.021	0.001	-0.113	-0.031	-0.080	0.021	<0.001	-0.121	-0.039
Prior partly alcohol-related hospitalisation										
last year	-0.069	0.026	0.008	-0.121	-0.018	-0.126	0.024	<0.001	-0.172	-0.080
over 1 year	-0.027	0.008	0.001	-0.043	-0.012	-0.043	0.006	<0.001	-0.056	-0.031
Prior non-CVD hospitalisation										
last year	-0.043	0.008	<0.001	-0.059	-0.026	-0.048	0.007	<0.001	-0.062	-0.033
over 1 year	-0.009	0.005	0.085	-0.020	0.001	-0.017	0.005	<0.001	-0.027	-0.008
Prior CVD hospitalisation										
last year	-0.134	0.022	<0.001	-0.178	-0.091	-0.109	0.026	<0.001	-0.160	-0.059
over 1 year	-0.078	0.009	<0.001	-0.097	-0.060	-0.097	0.010	<0.001	-0.115	-0.078
Scottish Index of Multiple Deprivation (SIMD)										
4th	0.006	0.008	0.445	-0.009	0.020	-0.018	0.007	0.007	-0.032	-0.005
3rd	-0.009	0.007	0.205	-0.024	0.005	-0.029	0.007	<0.001	-0.043	-0.016
2nd	-0.020	0.008	0.013	-0.037	-0.004	-0.049	0.007	<0.001	-0.063	-0.035
1st (Most deprived)	-0.048	0.008	<0.001	-0.064	-0.032	-0.077	0.007	<0.001	-0.091	-0.063
Constant	0.895	0.012	<0.001	0.872	0.918	0.904	0.012	<0.001	0.880	0.928
R^2 mean (min-max)	0.089	(0.077- 0.109)				0.125	(0.107- 0.153)			
Adjusted R^2 (min-max)	0.087	(0.074- 0.106)				0.123	(0.105- 0.151)			

*Covariate reference: aged 18 years, predicted AUDIT score =0, least deprived (5th SIMD), and no prior hospitalisation

5.4 Discussion

This chapter presents the estimation of HRQoL scores using SF-6D (SF-12) preferences-based index of different alcohol drinking status classified by the AUDIT score. The results show that current non-drinkers, i.e. those who have never consumed alcohol before and former drinkers reported worse HRQoL scores than low-risk drinkers, while high-risk drinkers who are probable alcohol dependent patients based on AUDIT showed the worst HRQoL compared to others. These findings further support the J-shaped morbidity curve, where those who have never consumed alcohol reported a worse HRQoL than low-risk drinkers (Petrie et al., 2008, Saarni et al., 2008, Valencia-Martin et al., 2013, Van Dijk et al., 2004). However, the published studies revealed the HRQoL score when other confounders were controlled for changed only small magnitude for those who had never consumed alcohol and low-risk drinkers. For the HRQoL of high-risk drinkers, the findings of the current study were consistent with those of previous studies; those also found that high-risk drinkers and alcohol-dependent patients had the worst HRQoL (Nogueira and Rodriguez-Miguez, 2014, Saarni et al., 2008, Petrie et al., 2008).

In addition, prior alcohol-related hospitalisations impacted the current HRQoL similar to prior CVD-related conditions in both males and females. However, this analysis might not be comparable to previous studies due to the different number of conditions included in the classification as this study included and other studies used for 8 to 47 alcohol-related conditions (Laramee et al., 2014, Jones and Bellis, 2014, Jones et al., 2008, Grant et al., 2009). Nevertheless, for females, wholly-alcohol related admission in the last year did not have any impact on the HRQoL because of the lack of event among females (only one case).

These findings have certain limitations. Firstly, selection bias and non-response bias of the health survey might be found since healthy people are more likely to be recruited in the health survey. At the same time, if unhealthy heavy drinkers were recruited, they would be less likely to respond regardless

of their alcohol drinking levels. As a result, the probability that this study lacks data from unhealthy people is high, which would underestimate the effect of high-risk drinking on health. The second limitation relates to the AUDIT score which was not measured in the SHeS 2003. The analysis required the use of a predicted AUDIT score to investigate the association between HRQoL and the AUDIT score for that year. Subsequently, the HRQoL scores were adjusted using the same covariates as the predicted AUDIT score, i.e. age and SIMD, since these covariates were also independently related to health status. Consequently, this might result in double adjusting.

Thirdly, HRQoL status might vary among individuals with the same health status since other variables related to health status were not taken into account in the analysis (e.g. marital status and smoking status). Even though other plausible confounders could not be controlled for, some covariates have been shown to have an effect on the relationship of alcohol drinking status and predicted AUDIT scores. Thus, excluding those variables seemed to reduce the overestimated effect of alcohol drinking on health, and the R-square values were very low in both male and female models. Lastly, the cross-sectional design of the health survey could not establish cause and effect. This is an important issue for further research interested in a health outcome measurement of alcohol drinking control intervention; therefore, these studies should prospectively investigate the change of HRQoL along with the AUDIT over time. Moreover, these studies should consider the measurements for alcohol use and HRQoL since they should be able to capture the effect of alcohol consumption on HRQoL unless it is found that the reduction of alcohol drinking risk does not show any significant improvement in HRQoL (Essex et al., 2014, UKATT Research Team, 2005b).

5.5 Conclusions

These results can be applied to the estimated HRQoL related to alcohol drinking pattern in terms of the AUDIT score. Moreover, the baseline HRQoL scores of the general population as well as the decrement of HRQoL scores involved in alcohol-related and non-alcohol related hospitalisations before the interview date can be used to develop an alcohol intervention model that processes QALY estimations.

Chapter 6: Development and validation of an alcohol intervention model for predicting life years

6.1 Introduction

In the past decade, public health policy makers have shown an increased interest in reducing alcohol-related harms through a wide range of alcohol policies and intervention (Babor et al., 2010b, Anderson et al., 2009a, Martineau et al., 2013, Room et al., 2003). The evaluation of alcohol policies and interventions has also become increasingly important - especially in terms of effectiveness and cost-effectiveness - to assess the achievement of those policies (Room et al., 2003). The expected outcomes of those interventions should be changes in epidemiological measures, e.g. mortality, morbidity, and health-related quality of life (HRQoL) in the population as well as in economic aspects where the impact of the intervention on costs can be considered (Tones, 1992, Martineau et al., 2013).

Nevertheless, it is still methodologically problematic to predict these final outcomes, especially when measured as LYs, QALYs, and lifetime economic costs - which are widely recommended for the purpose of health intervention economic evaluations (ISPOR, 2014, NICE, 2013, Chaikledkaew and Kittrongsiri, 2014, Teerawattananon and Chaikledkaew, 2008). Moreover, conducting RCTs for evaluation of these outcomes would likely not be practical for measuring long-term outcomes due to the limited follow-up period and large investment required for conducting RCTs. Thus, modelling studies are often necessary to predict longer-term outcomes (Briggs et al., 2006c, Drummond MF et al., 1997, Gray et al., 2011a). Chapter 2 also highlighted the limitations of previous alcohol modelling studies and the rationale behind developing this current alcohol intervention model. In this study, the term “alcohol intervention model” is used and defined as a model that can evaluate the long-

term effectiveness and cost-effectiveness of alcohol interventions to inform health policy decision-making (Lewsey et al., 2015).

The aim of this chapter is to describe the development and validation of the Scottish alcohol intervention model for predicting health outcomes in terms of LYs for different selected risk profiles related to alcohol consumption. Firstly, the conceptualisation and model structure of the alcohol intervention model used for alcohol intervention evaluation are specified to demonstrate all plausible events of the SHeS cohort. Secondly, the SHeS-SMR linkage data set will be analysed using three stages of data modelling. The statistical modelling approach will be applied for the development of the cause-specific hazard functions of plausible first events after the survey date and death following hospitalisation. Observed events and predicted events will then be compared to assess the model's performance. Thirdly, the predicted survival of the study cohort will be compared to the Scottish life table to calibrate the model. Finally, predicting life expectancy will be estimated using the health state transition model and cause-specific hazard models of the different individual risk profiles.

6.2 Methods

6.2.1 Conceptualisation of alcohol intervention model

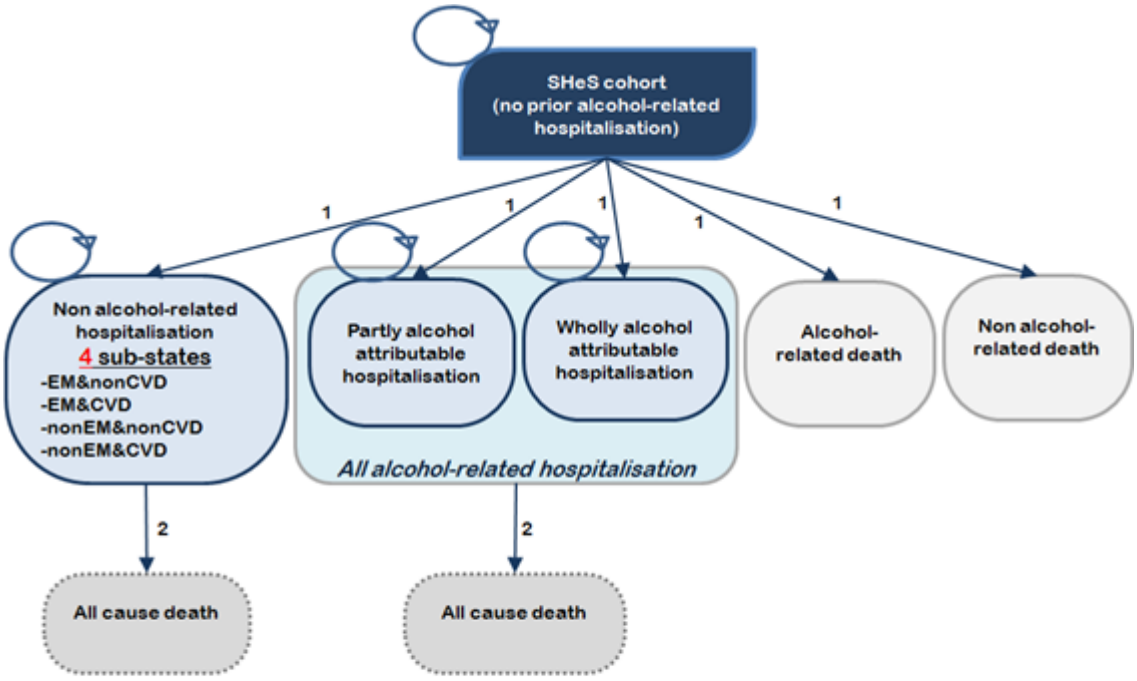
To estimate the long-term effects of alcohol intervention on LYs, QALYs, and lifetime costs, alcohol-related morbidity and mortality were investigated using the alcohol intervention model. To factor in the range of related risk factors that would likely affect alcohol-related hospitalisations and death, developing the intervention model of alcohol-related harms not only focussed on the association between drinking patterns and harms caused by alcohol but also on other related factors to predict the LYs and QALYs of different health risk profiles. These risk factors were identified as the pattern and level of alcohol consumption, socioeconomic status (Probst et al., 2015a, Jones et al., 2015b), and other factors which were found to have a relationship with alcohol drinking such as smoking status (Aekplakorn et al., 2008, De Leon et al., 2007,

Falk et al., 2006, Harrison et al., 2008, McKee et al., 2010), physical activity (Kendzor et al., 2008), and body mass index or BMI (Hart et al., 2010).

This study investigated alcohol-related and non-alcohol related hospitalisations and deaths among alcohol drinking patterns as well as other selected health risk factors. The linkage data set which was linked between the routine national health surveys and health administration records was employed to examine whether the selected risk factors would accurately predict hospitalisation and death. Then, the model of alcohol-related harms would be developed to estimate LYs, QALYs, and lifetime healthcare costs, and those outcomes would be presented in different risk profiles. Moreover, the findings could be used for the evaluation of interventions which aim to change those selected risk factors, and it could also show the association between the modified risk factors (intermediate outcome) and the final health outcomes of interest.

6.2.2 Health state transition model

This section summarises the overview of the health state transition model (more details are described in section 3.5 of Chapter 3:). The study cohort was a participant of the general population who had never experienced an alcohol-related hospitalisation prior to the survey date. Then, the structure of the alcohol intervention model (**Figure 6-1**) was defined as the key features of first competing consequences after the interview date. To estimate alcohol-related harms of different drinking patterns including other selected risk factors (equation 1), alcohol attributable hospitalisations and deaths identified by AAF were used, i.e. wholly alcohol-attributable conditions and partly alcohol-attributable conditions (Appendix 1). Moreover, other non-alcohol related hospitalisations and deaths were considered to be a competing risk of first events after the survey date; these events were categorised by emergency/non-emergency admission and cardiovascular diseases (CVD)/non-CVD defined by the ICD-9 and ICD-10 codes. The follow-up time for each participant was defined as the time from the initial interview date until either the date of occurring first events or until 31st December 2013 (censoring date).



Equation 1: Function (age at survey date, alcohol drinking status at survey date i.e. AUDIT (0-40) & binge drinking (Y/N), cigarette per day, CVD condition (Y/N), diabetes (Y/N), general health condition (GHQ score), physical activity, BMI, Prior other hospitalisation, SIMD) subgroup by gender
Equation 2: Function (age at first hospitalisation, CVD condition (Y/N), diabetes (Y/N), SIMD) subgroup by gender

SHeS: Scottish Health Survey, EM: Emergency admission, CVD: Cardiovascular disease

Figure 6-1 Structure of the alcohol-related harms health state transition model

For estimating LYs and QALYs, this analysis also factored in all-cause deaths after patients experienced the first hospitalisations (equation 2). Thus, the follow-up time for each hospitalised patient was defined as the time from their date of first hospitalisation until either the date of death or until 31st December 2013 (censoring date). Males and females were modelled separately for all analyses.

6.2.3 Data sources: SHeS-SMR/NRS linkage data

As described in section 3.7 of Chapter 3:, the electronic Data Research and Innovation Service (eDRIS) links the consented SHeS participant data set to SMR/NRS records via personal information using established probability matching techniques (Information Services Division). This study used the SHeS-SMR/NRS linkage data where the SHeS data sets from 1995, 1998, 2003, and

2008-2012 were linked to the SMR/NRS records, particularly SMR01 (inpatients and day cases) and mortality, and follow-up from year 1981 to the end of year 2013 as shown in **Figure 6-2**. This study protocol was approved by the NHS National Services Scotland Privacy Advisory Committee for accessing the SMR/NRS linkage data set through the national data security system or Safe Haven provided by the eDRIS (Information Services Division). Researchers able to access individual patient data must have undergone appropriate training necessary for obtaining an 'approved researcher' status (Appendix 3).

The selected covariates related to the baseline characteristics of the study cohort were derived from 8 survey years of the SHeS (see details in section 3.7.1 of Chapter 3:); these were age at survey date, gender, SIMD, alcohol consumption including the AUDIT score and binge drinking, smoking status (i.e. the number of cigarettes per day), health condition (i.e. having CVD and diabetes), physical activity, and BMI. In addition, prior non-alcohol related hospitalisation was designated as the SHeS cohort baseline characteristic so the SMR records (see details in section 3.7.2 of Chapter 3:) of individually consenting SHeS respondents before the interview date were used to define prior non-alcohol related hospitalisation. The SMR records were also used for identifying hospitalisation after the interview date, and the NRS mortality records were used to track the deaths of consenting SHeS participants.

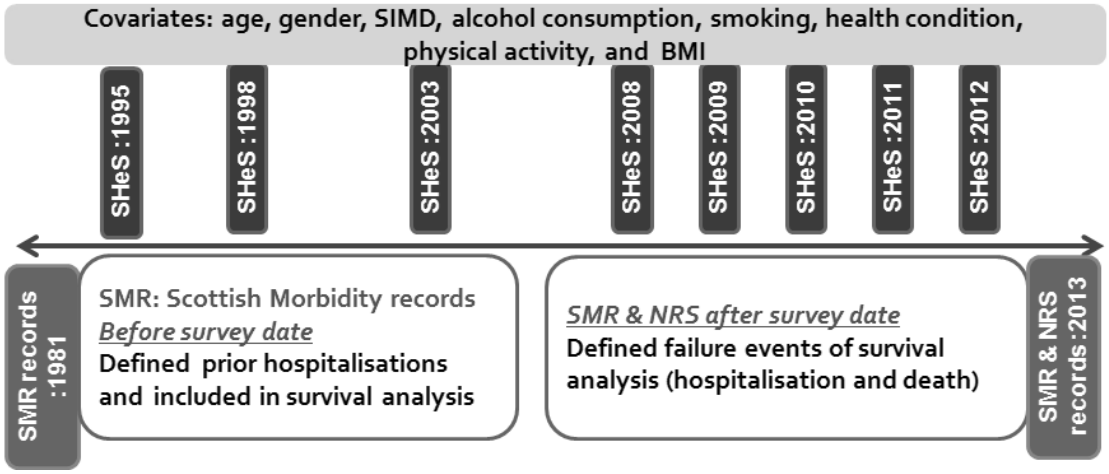


Figure 6-2 Scottish Health Survey (SHeS)/Scottish Morbidity Records (SMR) linkage data set

6.2.4 Adjusting under-reported alcohol unit consumption

The assessment of self-reported alcohol consumption typically indicates deliberate under-reporting, so previous studies suggested adjusting for under-reported consumption in the surveys using per capita sales data (Babor et al., 2010a, Meier et al., 2013). Therefore, this study employed adjusting for under-reported units consumed from the self-reported alcohol consumption of the SHeS data using a technique from a published study (Boniface and Shelton, 2013). Boniface and Shelton's study investigated the implications of under-reporting for alcohol consumption among the respondents of national private household surveys 2008 in England. It adjusted for under-reporting of consumption using a multiplying factor derived from matching alcohol sales data. Although under-reporting is also likely to vary by demographic and social factors, there is no evidence to suggest the magnitude or the direction of these associations. Based on available evidence, a previous study generated three scenarios of under-reporting adjusted (Boniface and Shelton, 2013): 1) an equal proportion of under-reporting among all drinkers based on comparison of survey and sales data; 2) heavy drinkers under-report proportionally more than light drinkers that recall accuracy is lower among heavier drinkers; and 3) alcohol consumption as a proportion of alcohol sales was calculated by drink type. Average weekly alcohol intake or heaviest drinking day in the last week was revised accordingly. The study concluded that adjusting under-report equally by 40% (scenario 1) could highlight the potential impact that underreporting has. For differentiated adjusting factor by drinking level (scenario 2) and type of alcohol beverage (scenario 3), scenario 2 showed over-estimates alcohol consumption (average weekly alcohol consumption exceeded per capita alcohol sales), and scenario 3 was very similar to scenarios 1.

As such, this study using the Scottish setting compared self-reported alcohol consumption (Hinchliffe, 2013) and UK sales data (HM Revenue and Customs, 2012, Robinson et al., 2013) of each year to generate the multiplying factors for adjusting under-reporting alcohol consumption as shown in Table 6-1. These multiplying factors were applied across all SHeS' participants to adjust for average weekly alcohol intake and units consumed on the heaviest

day so binge drinking could be reclassified after adjustment. The predicted AUDIT scores would be also adjusted since the weekly units consumed and units consumed on the heaviest day were the covariates of the predicted AUDIT scores (see details in Chapter 4:). However, non-drinkers are not included in the revision. Assessing misclassification of self-reported non-drinkers was beyond the scope of this study.

Table 6-1 Comparison of self-reported alcohol consumption (SHeS) and UK sales data to calculate under-reporting level

Year	UK sales data[a]		SHeS[b]	Under-reporting level	Multiplying factor[c]
	Litre of pure alcohol per adult (aged+16)	Unit per adult	Unit per week per adult (aged +16)		
1995	9.71 (1994/95)	18.64	13	30.3%	1.43
1998	10.15 (1997/98)	19.49	12.5	35.9%	1.56
2003	11.43 (2002/03)	21.94	14.1	35.7%	1.56
2008	11.51 (2007/08)	20.5	13.1	36.1%	1.56
2009	10.66 (2008/09)	20.46	12.4	39.4%	1.65
2010	10.83 (2009/10)	20.79	11.6	44.2%	1.79
2011	10.53 (2010/11)	20.21	11.1	45.1%	1.82
2012	10.24 (2011/12)	19.65	11.3	42.5%	1.74

a. HM Revenue and Customs. (2012). Table 2.3 Alcohol clearances per adult (1986/87-2010/11). Alcohol factsheet: March 2012: Office for National Statistics.

b. Hinchliffe, S. (2013). Chapter 3: Alcohol Consumption. In L. Rutherford, S. Hinchliffe & C. Sharp (Eds.), The Scottish Health Survey: 2012 edition Volume 1 Main Report: A National Statistics Publication for Scotland: The Scottish Government.

c. Boniface, S., & Shelton, N. (2013). How is alcohol consumption affected if we account for under-reporting? A hypothetical scenario. Eur J Public Health.

6.2.5 Data modelling

Modelling stage I: Estimating risk of having first events

During the follow-up period, a Cox proportional hazard model (Cox, 1972) - a semi-parametric method - was used to model the cause-specific hazard functions of the 8 competing first events as mentioned above (presented as equation 1 in **Figure 6-1**). For extrapolation beyond the period of follow-up, parametric proportional hazard models were also used (Cleves et al., 2010, Gray et al., 2011a, Hosmer et al., 2008). The causes of hospitalisations and deaths were classified by the ICD-9 and ICD-10 in Appendix 1 (Jones and Bellis, 2014, Jones et al., 2008, Grant et al., 2009). A Gompertz parametric regression survival analysis was used to model the cause specific hazards of the competing first events - defined as an event whose occurrence precludes or alters the probability of occurrence of a main event under examination (Cleves et al., 2010, Gray et al., 2011a, Hosmer et al., 2008, Putter et al., 2007, Coviello and Boggess, 2004); the Gompertz is the standard choice when modelling the risk of death (Gray et al., 2011a). The selected risk factors used for modelling the first events were age at survey date, alcohol drinking status at survey date with adjusted under-reporting alcohol consumption, i.e. the AUDIT score (0-40) and binge drinking (Y/N), number of cigarettes per day, CVD condition (Y/N), diabetes (Y/N), general health condition (3 groups of GHQ score), physical activity (no activity/low activity/medium activity/high activity), BMI (underweight/normal or BMI<25, overweight or BMI 25≤BMI<30, obesity or BMI≥30), prior non-alcohol related hospitalisation, and SIMD quintile (Office of the Chief Statistician, 2004). Males and females were modelled separately for all analyses since the reviewed literature reported that males and females have diverse alcohol drinking risks, morbidity, and mortality risk related to alcohol drinking (Schulte et al., 2009, Probst et al., 2015b, Richman et al., 1995).

For the Cox proportional hazard model (Cox, 1972), the hazard function $h(t|x_i)$ of each competing first event for the ith individual in the data is

$$h(t|x_i) = h_0(t)\exp(x_i\beta_x)$$

where $h_0(t)$ is the baseline hazard of each event and β_x are the regression coefficients indicating the effect of each covariate x_i. The baseline hazard is the hazard when all x_i=0 as the relative hazard is equal to one (Cleves et al., 2010, Gray et al., 2011a).

For extrapolation beyond the period of follow-up, a parametric proportional hazard model using a Gompertz regression was also considered (Cleves et al., 2010, Gray et al., 2011a), and the function of baseline hazard $h_0(t)$ is illustrated as:

$$h_0(t) = \exp(\beta_0)\exp(\gamma t)$$

where γ is the ancillary shape parameter estimated from the data. A Gompertz model allows for flexible specification of the hazard: when $\gamma > 0$ the hazard is increasing with time and when $\gamma < 0$ the hazard is decreasing with time. The models can then be reduced to the exponential model, i.e. hazards constant over time if $\gamma = 0$. Then, the function of the baseline hazard of exponential model is shown as:

$$h_0(t) = \exp(\beta_0)$$

Furthermore, the cause-specific hazard function derived from the parametric proportional hazard model would be used to estimate the predicted cumulative incidence $CI(t)$ of first event k as follows:

$$CI_k(t) = \sum p_k(t_u)$$

where $\sum p_k(t_u)$ is the cumulative sum of the unconditional probabilities of occurring first event k at time t_u up to and including time t. The unconditional probabilities are derived from:

$$p_k(t_u) = h_k(t_u)S(t_{u-1})$$

where $h_k(t_u)$ is the cause specific hazard of event k as derived from the parametric models. $S(t)$ is the survival function from any 8 competing events k at time t as shown below:

$$S(t) = \sqcap (1 - \sum h_k(t_j))$$

where $\sum h_k(t_j)$ is the sum of the eight cause specific hazards at time t.

All statistical analyses were performed using STATA version 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP). Two-sided tests with a *p*-value of less than 0.05 was considered statistically significant.

Modelling stage II: Estimating survival following hospitalisations

A Gompertz model was also used to model the hazard functions of all-cause deaths following the first hospitalisation classified as alcohol-related and non-alcohol related hospitalisations (presented as equation 2 in Figure 6-1). The covariates for modelling the cause-specific death were age at first hospitalisation, CVD condition (Y/N), diabetes (Y/N), and SIMD quintile (Office of the Chief Statistician, 2004); these were grouped by gender. A predicted survival curve of different risk profiles was extrapolated until the probability of surviving beyond the follow-up time point became zero; this was classified by gender and condition of the first hospitalisation. The area under the predicted survival curve was used to estimate the remaining life expectancy using the trapezoidal rule with half cycle correction (Gray et al., 2011a).

Modelling stage III: Estimating total life years

The health state transition model (**Figure 6-1**) with a one-year cycle period for 100 years was developed using Microsoft Excel® (Microsoft Corp., Redmond, WA). At the end of a model cycle, an individual risk profile can either remain in the no-event state or move to one of the first eight competing events,

i.e. hospitalisation or death states. There were three stages to estimate overall LYs of individual risk profiles. Firstly, the health state transition model estimated LYs remaining upon entering model (after the survey date) for each competing event that occurred. To calculate for these remaining LYs for each of the eight events, the analysis model summed the survival time before the first events (derived from Modelling stage I), and the survival time of following hospitalisations (derived from Modelling stage II) of each respective event. Secondly, the probability of having each first event within an annual cycle was estimated using the cause-specific hazard models; the sum of these estimated probabilities across all 100 cycles is always equal to 1. Thirdly, the LYs from the first stage were weighted by the probabilities of having a particular event from the second stage, and the remaining LYs adjusted by probabilities of having the event were summed. Finally, to estimate the overall LYs of the survey cohort in a particular risk profile, the additional LYs were combined with the age at survey date.

6.2.6 Dealing with missing data

A multiple imputation approach using chained equations was employed to fill missing data (Little and Rubin, 2002, Royston and White, 2011). The information in the observed values of the covariates was used to predict the missing values. To apply this method to this study - which investigates alcohol-related hospitalisations and deaths among SHeS-SMR/NRS linkage data due to the limitation of additional external information - missing at random (MAR) was assumed to impute missing data based on all predictors used in the survival analysis. As suggested by Royston and White (2009), this analysis also included the follow-up status and the Nelson-Aalen estimate of the cumulative hazard to the survival time as predictor covariates for the regression models (White and Royston, 2009). Once 100 imputed complete data sets were created and analysed, the results were combined using standard rules (Rubin, 1987).

6.2.7 Assessment of model performance

The developed model is considered to be a theoretical representation of a complex problem, and hence underwent a validation process that included measuring how accurately the model could represent 'real world' patterns. This important validation step helps build confidence in the structure and predictions of the model. For discrimination of the cause-specific hazard model, Harrell's C statistic was used (Steyerberg, 2009); this was proposed as measures of the general predictive discrimination of a survival regression model by Harrell et al. (Harrell et al., 1982, Harrell et al., 1996). The Harrell's C statistic estimates the probability of concordance between predicted and observed responses. A value of 0.5 indicates no predictive discrimination and a value of 1.0 indicates perfect discrimination of the study population with different outcomes (Harrell et al., 1982, Harrell et al., 1996).

It is noted that this study only assessed the discrimination compared between observed events – which occurred starting from the interview date to 31st December 2013 (censoring date) – and the model-predicted events during this period. Thus, this analysis is unable to determine how well the model could predict the event in the extrapolated period (beyond the censored date). Predicted life expectancies were obtained from the model where the risk factors were provided using the average values from the SHeS-SMR/NRS linkage data. Then, to calibrate the survival curve derived from the model, a calibration factor (range from 0-1) was applied for adjusting the linear predictor of the model, separated into male and female models. The predicted life expectancies of males and females were compared with the Scottish life table (National Records of Scotland, 2014), and a squared-error loss function (corresponding to the root mean square error, or RMSE) was calculated to select the calibration factors that minimise RMSE.

6.3 Results

6.3.1 Baseline characteristic of the study population

Table 6-2 presents the baseline characteristic of consenting SHeS participants from 1995, 1998, 2003, and 2008-2012, where individual survey information was linked with the SMR and death records of the NRS during the corresponding survey year. For the health state transition modelling analysis, SHeS participants who had no prior alcohol-related hospitalisation were defined as the initial health state of cohort. There were 46,230 SHeS participants (20,729 males and 25,501 females) with an average age of 47 years for both males and females. Most of participants were current drinkers (91% for males and 86% for females) with an average weekly drinking unit of 17 and 7 for males and females, respectively; these were adjusted for under-reported alcohol consumption using alcohol sales data. The average AUDIT score and binge drinking proportion of males was higher than females for both unadjusted and adjusted data. For smoking status, males and females were very similar in terms of the proportion of current smokers (28% for males and 26% for females) and number of cigarettes per day (5 for males and 4 for females). Approximately one-third had CVD in both male and female participants, and less than 5% of them had diabetes. A representative sample of Scotland was approximately 20% in each SIMD quintile. Additionally, 61% of males and 56% of females reported best general health condition as measured by the GHQ score. The highest proportion (40%) of physical activity was reported at the high level for males and medium level for females. Of all participants that measured BMI, two-thirds of the total population were classified as overweight (39% for males and 30% for females) and obese (23% for males and 24% for females). Over half of the respondents experienced non-alcohol related hospitalisation before the survey date.

Table 6-2 Demographics of SHeS participants who had no prior alcohol-related hospitalisation

	Males		**Females**	
Cohort size	20,729		25,501	
Age (years)	47.2	(17.4)	47.3	(17.7)
Drinking status				
Never drinker	732	4%	1828	7%
Former drinker	1042	5%	1650	6%
Current drinker	18834	91%	21891	86%
missing	*121*		*132*	
Average weekly drinking unit (include non-drinker)	17.1	(23.7)	7.13	(11.5)
Grouped weekly drinking unit				
0	1,915	9.2%	3,717	14.6%
>0-10	7,873	38.0%	15,446	60.6%
>10-20	4,523	21.8%	3,807	14.9%
>20-30	2,797	13.5%	1,363	5.3%
>30-40	1,299	6.3%	455	1.8%
>40-50	857	4.1%	291	1.1%
>50-60	448	2.2%	85	0.3%
>60-70	267	1.3%	61	0.2%
>70-80	166	0.8%	22	0.1%
>80-90	128	0.6%	15	0.1%
>90-100	71	0.3%	11	0.0%
>100	203	1.0%	31	0.1%
missing	*182*		*197*	
AUDIT score				
SHeS 2012 (observed value)	5.1	(4.6)	3.4	(3.7)
n	*1,469*		*1,787*	
SHeS 1995-2011 (predicted value)	5.4	(3.8)	3.1	(2.8)
n	*16,755*		*20,518*	
missing	*2,505*		*3,196*	
Binge drinking (included non-drinker)	5,054	24%	3,325	13%
missing	*333*		*467*	

**Statistics are mean (SD).*

Table 6-2 Demographics of SHeS participants who had no prior alcohol-related hospitalisation (cont.)

	Males		Females	
Adjusted under-reported				
Average weekly drinking unit (include non-drinker)	27.7	(38.3)	11.7	(18.9)
Grouped weekly drinking unit (units)				
0	1,915	9.2%	3,717	14.6%
>0-10	5,790	27.9%	12,338	48.4%
>10-20	3,213	15.5%	4,322	16.9%
>20-30	2,941	14.2%	2,265	8.9%
>30-40	1,973	9.5%	1,093	4.3%
>40-50	1,405	6.8%	581	2.3%
>50-60	857	4.1%	332	1.3%
>60-70	663	3.2%	179	0.7%
>70-80	439	2.1%	221	0.9%
>80-90	326	1.6%	75	0.3%
>90-100	225	1.1%	43	0.2%
>100	800	3.9%	138	0.5%
AUDIT score	6.8	(5.4)	4.1	(4.2)
Binge drinking (included non-drinker)	8,449	40.8%	7,315	28.7%
Smoking status				
Never smoke	8,594	41.5%	11,945	46.8%
Ex-smoker	6,264	30.2%	6,738	26.4%
Current smoker	5,830	28.1%	6,760	26.5%
missing	*41*		*58*	
Cigarette per day	4.5	(9.2)	3.8	(7.5)
missing	*214*		*123*	

**Statistics are mean (SD).*

Table 6-2Demographics of SHeS participants who had no prior alcohol-related hospitalisation (cont.)

	Males		Females	
Having CVD	6,424	31.0%	7,639	30.0%
Having diabetes	1,000	4.8%	960	3.8%
SIMD quintile				
1st (most deprived)	4,043	19.5%	5,385	21.1%
2nd	4,098	19.8%	5,157	20.2%
3rd	4,387	21.2%	5,280	20.7%
4th	4,501	21.7%	5,239	20.5%
5th(least deprived)	3,683	17.8%	4,422	17.3%
missing	*17*		*18*	
GHQ score				
Score 0 (best)	2,737	61.4%	14,318	56.1%
Score 1-3	4,700	22.7%	6,111	24.0%
Score 4+ (worst)	2,452	11.8%	4,013	15.7%
missing	*840*		*1,059*	
Physical activity				
No activity	3,316	16.0%	4,403	17.3%
Low activity	2,458	11.9%	2,936	11.5%
Medium activity	6,823	32.9%	10,321	40.5%
High activity	8,114	39.1%	7,804	30.6%
missing	*18*		*37*	
BMI (mean, SD)	27.3	(4.6)	27.4	(5.7)
<25	6,236	30.1%	8,821	34.6%
25- <30 (overweight)	7,991	38.5%	7,610	29.8%
>=30 (obesity)	4,758	23.0%	6,167	24.2%
missing	*1,744*		*2,903*	
Prior non-alcohol related hospitalisation				
No hospitalisation	6,889	33.2%	7,542	29.6%
within last year	2,450	11.8%	3,035	11.9%
over 1 year	11,435	55.2%	14,924	58.5%

**Statistics are mean (SD).*

Table 6-3 illustrates the observed events of SHeS cohorts who had no prior alcohol-related hospitalisation. These events were indicated using SMR/NRS records starting from the interview date to 31st December 2013 with the maximum follow-up period of 19 years. For both males and females, approximately 50% of the cohorts had first-observed events (8 competing first events) during the follow-up period. The highest proportion of those first events was non-emergency admission and non-CVD condition (25% vs. 29%, males vs. females) followed by emergency admission and non-CVD condition (15% vs. 15%), partly alcohol attributable hospitalisation (1.8% vs. 2.3%), and emergency admission and CVD condition (2.4% vs. 1.3%). Following the first alcohol-related hospitalisation (445 events for males and 614 events for females), the total number of deaths were 133 males (30% of hospitalised patients) and 119 females (19% of hospitalised patients). For non-alcohol related hospitalised patients (9,053 males and 11,666 females), the total death post-hospitalisation were 1,296 males (14% of those patients) and 1,426 females (12% of those patients).

Table 6-3 Hospitalisation and death events after survey date until 31st December 2013

	Males	**(20,729)**	**Females**	**(25,501)**
	Number	**% of baseline cohort**	**Number**	**% of baseline cohort**
Alive and no event	11,005	53.1%	13,024	51.1%
First events				
Wholly alcohol attributable hospitalisation	68	0.3%	38	0.1%
Partly alcohol attributable hospitalisation	377	1.8%	576	2.3%
Emergency admission and non-CVD condition	3,090	14.9%	3,805	14.9%
Emergency admission and CVD condition	507	2.4%	343	1.3%
Non-emergency admission and non-CVD condition	5,198	25.1%	7,369	28.9%
Non-emergency admission and CVD condition	258	1.2%	149	0.6%
Alcohol-related death	47	0.2%	44	0.2%
Non-alcohol related death	179	0.9%	153	0.6%
Death following first hospitalisation				
Death post alcohol-related hospitalisation	133	0.6% (30% of alcohol-related patients)	119	0.5% (19% of alcohol-related patients)
Death post non-alcohol related hospitalisation	1,296	6.3% (14% of non-alcohol related patients)	1,426	5.6% (12% of non-alcohol related patients)

Figure 6-3 and Figure 6-4 illustrate the graphs of observed cumulative incidence of first events after the survey date over a 19-year follow-up period classified by gender. The graphs reveal that emergency and non- emergency admission with non–CVD gradually increased the cumulative incidence until the end of the follow-up period, and the incidence of these events were higher than other events which likely remained steady over time.

Figure 6-3 Observed cumulative incidence of first events: males

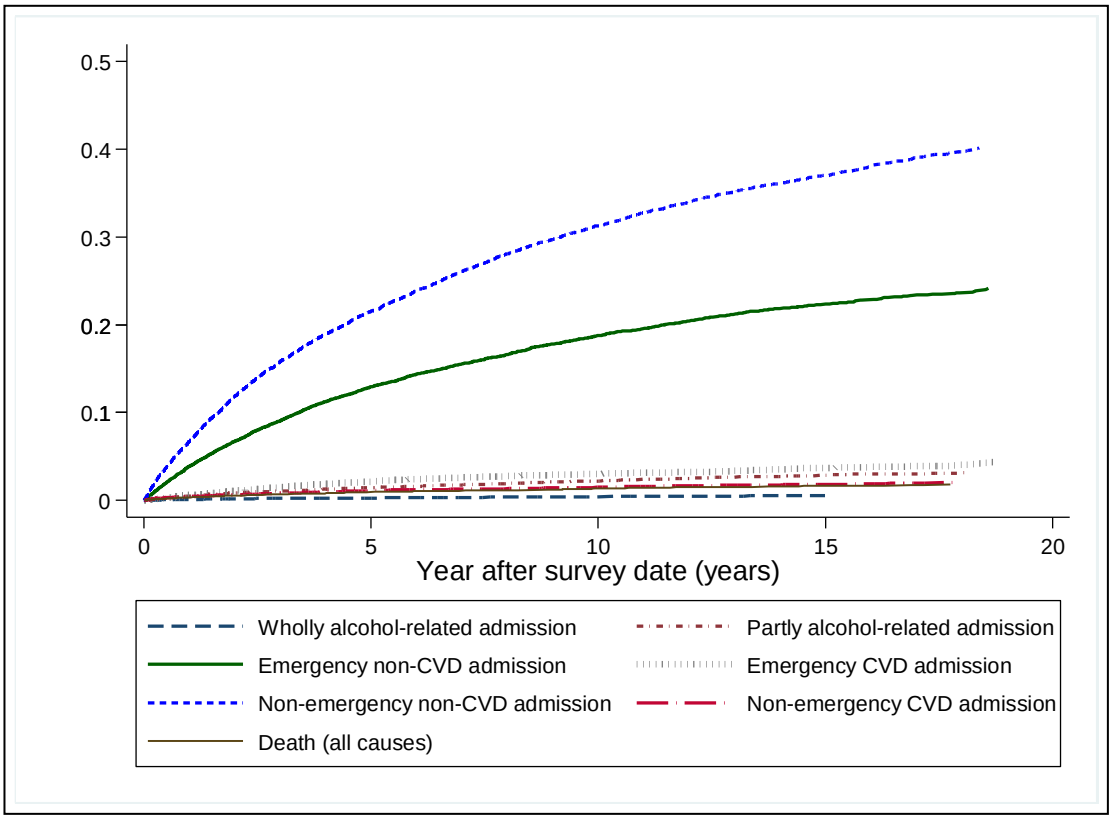
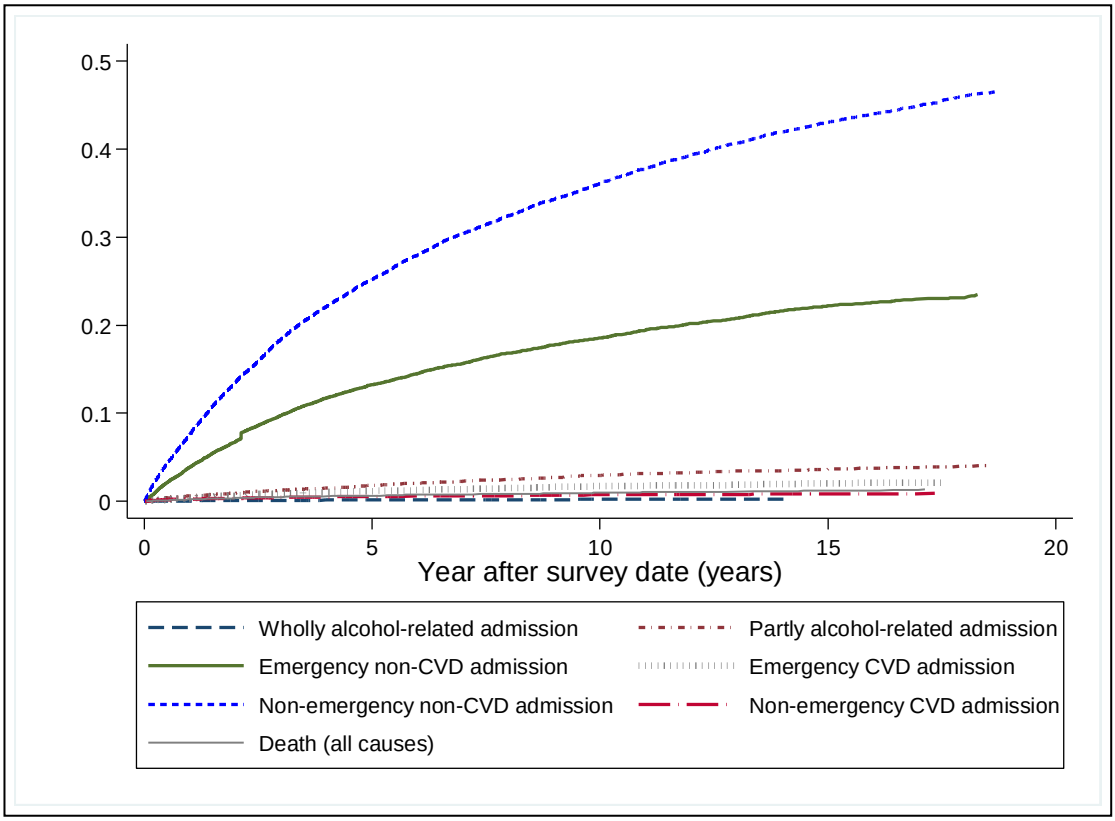


Figure 6-4 Observed cumulative incidence of first events: females



6.3.2 Modelling stage I: Risk of having first events

The hazard ratios (HRs) of having each first event are shown in Table 6-4, Table 6-5, Table 6-6, and Table 6-7, classified by gender and alcohol-attributable conditions. All cause-specific hazard ratios were derived from a Gompertz regression and multiple imputation using chained equations. The modifiable risk factors were selected to fit the model, i.e. alcohol consumption (AUDIT score and binge drinking), number of cigarettes per day, BMI, and physical activity. The results revealed that the selected modifiable risk factors likely affected the risk of first events (i.e. hospitalisation and death) after the survey date. When other covariates were adjusted, the HRs of an increase in the unit of AUDIT score were: 1.062 for males (95% CI [1.022, 1.102], p=0.002) for wholly alcohol-attributable hospitalisation, 1.021 (95% CI [0.994, 1.049], p=0.132) for partly alcohol-attributable condition, 1.049 (95% CI [0.997, 1.104], p=0.066) for alcohol-related death, and 1.013 (95% CI [1.004, 1.022], p=0.007) for emergency admission and non-CVD condition. For females, there were no statistically significant increasing risks of having those events for a unit increase in the AUDIT score. Binge drinking was also not shown to be an increasing risk of hospitalisation and mortality among SHeS participants.

An increase in the number of cigarettes per day was found to be significant in increasing risks of alcohol-related events for both males and females. For wholly alcohol–attributable hospitalisations, HRs were 1.029 (95% CI [1.018, 1.040], p<0.001) for males and 1.045 (95% CI [1.018, 1.074], p=0.001) for females. For partly alcohol–attributable hospitalisations, HRs were 1.012 (95% CI [1.004, 1.020], p=0.004) for males and 1.015 (95% CI [1.005, 1.025], p=0.002) for females. For alcohol–related death, HRs were 1.018 (95% CI [0.999, 1.038], p=0.062) for males and 1.044 (95% CI [1.017, 1.072], p=0.001) for females. Moreover, the increase in cigarettes per day revealed an increase in risk of non–alcohol related events in males at a p-value<0.001. HRs were 1.008, 95% CI [1.005, 1.011] for emergency admission and non-CVD condition, 1.024, 95% CI [1.019, 1.030] for emergency admission and CVD condition, and 1.020, 95% CI [1.012, 1.029] for non-alcohol related death. Likewise, for females, HRs of increasing cigarettes per day were 1.011 (95% CI [1.008, 1.015], p<0.001) for

emergency admission and non-CVD condition, 1.041 (95% CI [1.030, 1.052], p<0.001) for emergency admission and CVD condition, 1.003 (95% CI [1.000, 1.006], p=0.027) for non-emergency admission and non-CVD condition, 1.026 (95% CI [1.007, 1.045], p=0.034) for non-emergency admission and CVD condition, and 1.053 (95% CI [1.037, 1.069], p<0.001) for non-alcohol related death.

When selecting explanatory variables to fit the model, BMI was included particularly for the Gompertz models of non-alcohol related hospitalisation but was excluded from the models of alcohol-related hospitalisation and death caused by alcohol-related and non-alcohol related factors. Being overweight (25≤BMI<30) was found to increase the risk of emergency admission and CVD condition with an HR value of 1.402 (95% CI [1.103, 1.781], p=0.006) for males and higher risk for females with an HR value 1.556 (95% CI [1.183, 2.048], p=0.002). Moreover, obese females (BMI≥30) was found to increase the risk of emergency admission with non-CVD condition (HR=1.147, 95% CI [1.052, 1.250], p=0.002). For non-emergency admission, there were different risks between overweight males and females. Overweight males had increased risk of having non-emergency admission with non-CVD condition (HR=1.112, 95% CI [1.039, 1.191], p=0.002) while overweight females were estimated to have double the risk of having non-emergency admission with CVD condition (HR=1.894, 95% CI [1.203, 2.981], p=0.006).

Physical activity was revealed to have positive effects on hospitalisations and deaths in both males and females. High physical activity was shown to decrease risk by approximately 35 % for partly alcohol-related hospitalisation (HR=0.671, 95% CI [0.479, 0.941], p=0.021 for males and HR=0.635, 95% CI [0.482, 0.837], p=0.001 for females). In addition, high physical activity decreased the risk of emergency CVD admission by 26% and 35% for males and females, respectively (HR=0.744, 95% CI [0.560, 0.990], p=0.042 for males and HR=0.647, 95% CI [0.449, 0.931], p=0.019 for females). All levels of physical activity significantly decreased the risk of emergency non-CVD admission, ranging from 29% to 46% at p-value<0.001 (HRs ranged from 0.690 to 0.716 for males and 0.537 to 0.649 for females). Moreover, for decreasing mortality risk,

all levels of physical activity reduced the risk of non-alcohol related death ranging from 43% to 61% at a *p*-value<0.01 (HR range of 0.391 to 0.573 for males and 0.291 to 0.542 for females). For females in particular, medium and high physical activity were also found to significantly decrease the risk of alcohol-related death (HR=0.183, 95% CI [0.058, 0.580], p=0.004 for high activity and HR=0.373, 95% CI [0.177, 0.785], p=0.009 for medium activity).

In addition, when considering hospitalisations and deaths among different socioeconomic status as measured by the deprivation index (most deprivation=1st SIMD quintile to least deprivation=5th SIMD quintile), less deprivations revealed benefits for alcohol-related and non-alcohol related events as well. For men, compared to the highest level of deprivation, people who were less deprived at the 4th SIMD quintile showed 55% less risk of only wholly alcohol-related hospitalisation (HR=0.450, 95% CI [0.208, 0.973], p=0.042), and the 3rd SIMD quintile revealed 74% less risk of alcohol-related death (HR=0.260, 95% CI [0.086, 0.783], p=0.017). However, deprivation had no effect on alcohol-related events in women. Moreover, deprivation showed effects on non-alcohol related conditions in both men and women. For emergency and non-CVD condition, lower deprivation presented less risk ranging from 12% to 30% for men and 20% to 37% for women at a highly significant level (p<0.001). Additionally, women with the least deprivation (5th SIMD quintile) was 67% less at risk from non-alcohol related death (HR=0.433, 95% CI [0.221, 0.848], p=0.015).

Furthermore, modifiable risk factors were selected to predict the cumulative incidence of having first event classified by gender after the follow-up period as shown in Figure 6-5 for males and Figure 6-6 for females. For males, the selected risk profile was aged 30 years, AUDIT score=10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior hospitalisation more than one year ago, and the best GHQ score. For females, the selected risk profile was aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, prior hospitalisation over last year, and the best GHQ score. The predicted cumulative incidence was consistent with the observed

cumulative incidence (Figure 6-3 and Figure 6-4), and it revealed that emergency and non-emergency admission with non–CVD condition gradually increased over time, with females showing a higher cumulative incidence than males. The incidence of those events was higher than other events which likely remained steady both males and females.

6.3.3 Assessment of model performance for predicting first events after survey date

Model discrimination of first events

For discrimination of the cause-specific hazard model, Harrell's C-statistic was assessed (Steyerberg, 2009, Harrell et al., 1996, Harrell et al., 1982), where the general predictive discrimination of models used selected modifiable risk factors as explanatory variables. This analysis showed that the model discriminated in the follow-up period. Harrell's C–statistic values of cause-specific hazard models are shown in Table 6-4, Table 6-5, Table 6-6, and Table 6-7, classified by gender and alcohol-related conditions. Harrell's C-statistic of models for alcohol-related first events ranged from 0.66 to 0.81, and the regression models of males predicted discrimination better than the females' models. Moreover, for non–alcohol related hospitalisations, the predictive discrimination of these models ranged from 0.63 to 0.87. The best predictive discrimination was the non-alcohol related death models with a Harrell's C-statistic value of 0.91 for males and 0.92 for females.

Internal validity of predicting first events

The cause-specific hazard models were internally validated by comparing the numbers of predicted and observed first events across the linear predictors quintile (e.g. the highest fifth of linear predictors are those individuals at highest risk). Table 6-8 and Table 6-9 present the compared events of alcohol-related conditions while Table 6-10 and Table 6-11 present the compared events of non-alcohol related condition classified by gender. Then, a pair t-test was used to determine whether there was a difference in the number of predicted events compared with the observed events across the risk quintile. As the p-values were more than 0.05 across all quintiles, it can be concluded that there was no difference in the number of predicted first events compared to observed first events.

Table 6-4 Cause-specific hazards of alcohol-related first event after survey date: males

	a) wholly alcohol-related hospitalisation				b) partly alcohol-related hospitalisation				c) alcohol-related death			
Covariate*	**Hazard ratio**	***p-value***	**95%CI**		**Hazard ratio**	***p-value***	**95%CI**		**Hazard ratio**	***p-value***	**95%CI**	
Age at survey date	0.999	*0.923*	0.981	1.018	1.055	*<0.001*	1.046	1.063	1.030	*0.010*	1.007	1.053
AUDIT score	1.062	*0.002*	1.022	1.102	1.021	*0.132*	0.994	1.049	1.049	*0.066*	0.997	1.104
Binge drinking	0.695	*0.259*	0.369	1.308	1.095	*0.528*	0.826	1.451	1.529	*0.271*	0.717	3.256
CVD	1.535	*0.135*	0.876	2.689	1.488	*0.001*	1.179	1.876	1.277	*0.491*	0.637	2.559
Diabetes	0.342	*0.294*	0.046	2.542	1.028	*0.900*	0.672	1.570	2.268	*0.117*	0.815	6.310
Cigarettes per day	1.029	*0.000*	1.018	1.040	1.012	*0.004*	1.004	1.020	1.018	*0.062*	0.999	1.038
Low physical activity	1.127	*0.765*	0.513	2.479	0.952	*0.782*	0.673	1.348	0.421	*0.138*	0.134	1.320
Medium physical activity	0.587	*0.143*	0.287	1.198	1.015	*0.920*	0.760	1.355	0.528	*0.127*	0.233	1.199
High physical activity	0.611	*0.194*	0.291	1.285	0.671	*0.021*	0.479	0.941	0.713	*0.432*	0.307	1.656
2nd SIMD	0.569	*0.099*	0.291	1.112	0.925	*0.641*	0.666	1.284	0.941	*0.868*	0.456	1.939
3rd SIMD	0.506	*0.057*	0.251	1.021	1.286	*0.100*	0.953	1.737	0.260	*0.017*	0.086	0.783
4th SIMD	0.450	*0.042*	0.208	0.973	0.734	*0.083*	0.518	1.041	0.509	*0.143*	0.206	1.257
5th SIMD (least deprived)	0.477	*0.073*	0.212	1.070	1.036	*0.832*	0.745	1.442	0.505	*0.162*	0.193	1.317
Hospitalised last year	1.602	*0.273*	0.690	3.717	1.672	*0.003*	1.191	2.349	4.419	*0.001*	1.897	10.292
Hospitalised over 1 year	1.354	*0.280*	0.781	2.346	1.235	*0.078*	0.976	1.563	1.440	*0.322*	0.700	2.965
GHQ score (1-3)	1.459	*0.231*	0.787	2.707	1.031	*0.817*	0.798	1.332	1.287	*0.492*	0.627	2.639
GHQ score (4+worse)	2.777	*0.001*	1.528	5.044	1.046	*0.795*	0.745	1.469	1.596	*0.254*	0.715	3.562
Constant	-7.452	*<0.001*	-8.786	-6.118	-8.906	*<0.001*	-9.595	-8.217	-9.755	*<0.001*	-11.540	-7.969
Gamma	-0.033	*0.324*	-0.099	0.033	0.043	*0.002*	0.016	0.070	0.038	*0.309*	-0.035	0.112
Harrell's C-statistic	0.814				0.758				0.752			

*Covariate reference: aged 16 years, AUDIT score=0, non-binge drinking, no CVD, no diabetes, non-smoking, no physical activity, most deprived (1st SIMD), no prior hospitalisation, and GHQ score=0 (best)

Table 6-5 Cause-specific hazards of non-alcohol related first event after survey date: males

	a) emergency admission and non-CVD condition				b) emergency admission and CVD condition			
Covariate*	**Hazard ratio**	***p-value***	**95%CI**		**Hazard ratio**	***p-value***	**95%CI**	
Age at survey date	1.017	*<0.001*	1.014	1.019	1.066	*<0.001*	1.058	1.074
AUDIT score	1.013	*0.007*	1.004	1.022	0.996	*0.746*	0.970	1.022
Binge drinking	0.853	*0.002*	0.771	0.943	1.020	*0.882*	0.785	1.326
BMI (25-<30)	0.936	*0.140*	0.857	1.022	1.402	*0.006*	1.103	1.781
BMI (>=30)	0.894	*0.032*	0.807	0.990	1.283	*0.075*	0.975	1.690
CVD	1.196	*<0.001*	1.095	1.305	1.732	*<0.001*	1.410	2.126
Diabetes	1.468	*<0.001*	1.266	1.703	1.537	*0.004*	1.152	2.050
Cigarettes per day	1.008	*<0.001*	1.005	1.011	1.024	*<0.001*	1.019	1.030
Low physical activity	0.716	*<0.001*	0.629	0.815	1.054	*0.710*	0.798	1.392
Medium physical activity	0.694	*<0.001*	0.625	0.770	0.926	*0.532*	0.728	1.178
High physical activity	0.690	*<0.001*	0.619	0.771	0.744	*0.042*	0.560	0.990
2nd SIMD	0.886	*0.022*	0.798	0.983	1.028	*0.832*	0.795	1.329
3rd SIMD	0.709	*<0.001*	0.636	0.791	0.820	*0.145*	0.628	1.071
4th SIMD	0.752	*<0.001*	0.674	0.839	0.795	*0.104*	0.602	1.049
5th SIMD (least deprived)	0.704	*<0.001*	0.626	0.791	0.728	*0.039*	0.539	0.983
Hospitalised last year	2.504	*<0.001*	2.231	2.811	1.681	*0.001*	1.252	2.256
Hospitalised over 1 year	1.548	*<0.001*	1.423	1.684	1.295	*0.018*	1.044	1.606
GHQ score (1-3)	1.170	*<0.001*	1.073	1.276	1.073	*0.540*	0.857	1.342
GHQ score (4+worse)	1.388	*<0.001*	1.251	1.541	1.249	*0.111*	0.951	1.641
Constant	-4.141	*<0.001*	-4.353	-3.930	-9.461	*<0.001*	-10.105	-8.816
Gamma	-0.021	*<0.001*	-0.031	-0.011	0.050	*<0.001*	0.025	0.075
Harrell's C-statistic	0.645				0.836			

*****Covariate reference: aged 16 years, AUDIT score=0, non-binge drinking, BMI<25, no CVD, no diabetes, non-smoking, no physical activity, most deprived (1st SIMD), no prior hospitalisation, and GHQ score=0 (best)

Table 6-5 Cause-specific hazards of non-alcohol related first event after survey date: males (cont.)

	c) non-emergency admission and non-CVD condition				d) non-emergency admission and CVD condition				e) Non-alcohol related death			
Covariate*	**Hazard ratio**	***p-value***	**95%CI**		**Hazard ratio**	***p-value***	**95%CI**		**Hazard ratio**	***p-value***	**95%CI**	
Age at survey date	1.023	*<0.001*	1.021	1.025	1.051	*<0.001*	1.040	1.062	1.095	*<0.001*	1.080	1.110
AUDIT score	1.0003	*0.946*	0.993	1.008	0.992	*0.665*	0.955	1.030	1.013	*0.579*	0.968	1.061
Binge drinking	0.921	*0.037*	0.853	0.995	1.074	*0.703*	0.744	1.551	0.896	*0.648*	0.560	1.434
BMI (25-<30)	1.112	*0.002*	1.039	1.191	1.140	*0.422*	0.829	1.568				
BMI (>=30)	1.027	*0.507*	0.948	1.113	0.882	*0.516*	0.605	1.288				
CVD	0.999	*0.976*	0.933	1.069	3.065	*<0.001*	2.273	4.133	1.464	*0.031*	1.035	2.070
Diabetes	1.197	*0.006*	1.053	1.360	1.215	*0.355*	0.804	1.834	1.452	*0.115*	0.913	2.307
Cigarettes per day	1.000	*0.789*	0.997	1.003	1.007	*0.208*	0.996	1.019	1.020	*<0.001*	1.012	1.029
Low physical activity	1.057	*0.289*	0.954	1.171	1.081	*0.692*	0.735	1.590	0.490	*0.006*	0.296	0.811
Medium physical activity	0.998	*0.956*	0.915	1.088	0.926	*0.657*	0.659	1.302	0.573	*0.004*	0.391	0.840
High physical activity	0.987	*0.782*	0.902	1.081	0.767	*0.186*	0.517	1.137	0.391	*<0.001*	0.236	0.650
2nd SIMD	1.038	*0.401*	0.951	1.133	0.793	*0.238*	0.540	1.165	0.831	*0.417*	0.530	1.301
3rd SIMD	1.007	*0.882*	0.923	1.097	0.800	*0.244*	0.549	1.165	0.844	*0.451*	0.542	1.313
4th SIMD	1.053	*0.238*	0.966	1.148	0.954	*0.802*	0.659	1.380	0.902	*0.652*	0.576	1.413
5th SIMD (least deprived)	0.933	*0.144*	0.851	1.024	0.812	*0.316*	0.540	1.220	0.748	*0.260*	0.452	1.239
Hospitalised last year	2.586	*<0.001*	2.369	2.823	2.484	*<0.001*	1.719	3.589	2.077	*0.011*	1.181	3.651
Hospitalised over 1 year	1.464	*<0.001*	1.373	1.561	1.086	*0.600*	0.798	1.476	2.322	*<0.001*	1.509	3.575
GHQ score (1-3)	1.225	*<0.001*	1.147	1.309	1.252	*0.149*	0.923	1.698	1.152	*0.475*	0.782	1.696
GHQ score (4+worse)	1.285	*<0.001*	1.179	1.400	1.662	*0.005*	1.166	2.368	1.883	*0.003*	1.241	2.855
Constant	-4.315	*<0.001*	-4.488	-4.143	-9.286	*<0.001*	-10.165	-8.406	-12.161	*<0.001*	-13.342	-10.981
Gamma	-0.029	*<0.001*	-0.037	-0.021	0.029	*0.109*	-0.007	0.065	0.098	*<0.001*	0.054	0.142
Harrell's C-statistic	0.657				0.852				0.911			

*****Covariate reference: aged 16 years, AUDIT score=0, non-binge drinking, BMI<25, no CVD, no diabetes, non-smoking, no physical activity, most deprived (1st SIMD), no prior hospitalisation, and GHQ score=0 (best)

Table 6-6 Cause-specific hazards of alcohol-related first event after survey date: females

	a) wholly alcohol-related hospitalisation				b) partly alcohol-related hospitalisation				c) alcohol-related death			
Covariate*	**Hazard ratio**	***p-value***	**95%CI**		**Hazard ratio**	***p-value***	**95%CI**		**Hazard ratio**	***p-value***	**95%CI**	
Age at survey date	0.996	*0.757*	0.974	1.020	1.031	*<0.001*	1.025	1.037	1.053	*<0.001*	1.029	1.078
AUDIT score	1.050	*0.165*	0.980	1.125	1.002	*0.916*	0.969	1.035	1.058	*0.172*	0.976	1.147
Binge drinking	0.808	*0.645*	0.327	1.999	0.901	*0.454*	0.685	1.184	0.919	*0.863*	0.354	2.389
CVD	1.466	*0.318*	0.692	3.106	1.131	*0.210*	0.933	1.371	1.103	*0.773*	0.565	2.153
Diabetes	0.719	*0.751*	0.093	5.545	0.978	*0.923*	0.629	1.522	0.863	*0.844*	0.199	3.744
Cigarettes per day	1.045	*0.001*	1.018	1.074	1.015	*0.002*	1.005	1.025	1.044	*0.001*	1.017	1.072
Low physical activity	0.407	*0.181*	0.109	1.517	0.962	*0.795*	0.721	1.285	0.349	*0.061*	0.116	1.050
Medium physical activity	0.420	*0.054*	0.174	1.014	0.789	*0.047*	0.624	0.997	0.373	*0.009*	0.177	0.785
High physical activity	0.616	*0.308*	0.243	1.564	0.635	*0.001*	0.482	0.837	0.183	*0.004*	0.058	0.580
2nd SIMD	0.582	*0.248*	0.233	1.457	0.841	*0.187*	0.650	1.088	1.248	*0.609*	0.534	2.916
3rd SIMD	0.846	*0.702*	0.360	1.992	1.021	*0.871*	0.794	1.313	1.044	*0.927*	0.418	2.606
4th SIMD	0.402	*0.117*	0.128	1.257	0.827	*0.161*	0.633	1.079	0.767	*0.616*	0.271	2.166
5th SIMD (least deprived)	0.481	*0.209*	0.153	1.506	1.058	*0.677*	0.813	1.376	1.128	*0.812*	0.418	3.048
Hospitalised last year	1.866	*0.277*	0.606	5.747	1.529	*0.005*	1.137	2.056	4.923	*0.008*	1.506	16.096
Hospitalised over 1 year	1.550	*0.278*	0.702	3.420	1.381	*0.001*	1.140	1.674	3.938	*0.006*	1.495	10.375
GHQ score (1-3)	1.130	*0.779*	0.482	2.645	1.149	*0.175*	0.940	1.404	0.874	*0.725*	0.412	1.855
GHQ score (4+worse)	2.243	*0.040*	1.036	4.857	1.265	*0.048*	1.002	1.598	1.108	*0.803*	0.494	2.487
Constant	-7.881	*<0.001*	-9.560	-6.202	-7.026	*0.000*	-7.531	-6.521	-11.726	*<0.001*	-13.777	-9.676
Gamma	-0.030	*0.515*	-0.120	0.060	0.024	*0.028*	0.003	0.045	0.099	*0.010*	0.023	0.175
Harrell's C-statistic	0.808				0.663				0.809			

*Covariate reference: aged 16 years, AUDIT score=0, non-binge drinking, no CVD, no diabetes, non-smoking, no physical activity, most deprived (1st SIMD), no prior hospitalisation, and GHQ score=0 (best)

Table 6-7 Cause-specific hazards of non-alcohol related first event after survey date: females

	a) emergency admission and non-CVD condition				b) emergency admission and CVD condition			
Covariate*	**Hazard ratio**	***p-value***	**95%CI**		**Hazard ratio**	***p-value***	**95%CI**	
Age at survey date	1.014	*<0.001*	1.012	1.017	1.072	*<0.001*	1.062	1.082
AUDIT score	1.003	*0.638*	0.991	1.015	0.943	*0.045*	0.890	0.999
Binge drinking	0.877	*0.014*	0.790	0.974	0.941	*0.792*	0.600	1.477
BMI (25-<30)	0.967	*0.449*	0.886	1.055	1.556	*0.002*	1.183	2.048
BMI (>=30)	1.147	*0.002*	1.052	1.250	1.058	*0.727*	0.771	1.451
CVD	1.234	*<0.001*	1.142	1.332	1.680	*<0.001*	1.311	2.153
Diabetes	1.324	*<0.001*	1.148	1.527	2.151	*<0.001*	1.537	3.011
Cigarettes per day	1.011	*<0.001*	1.008	1.015	1.041	*<0.001*	1.030	1.052
Low physical activity	0.649	*<0.001*	0.580	0.727	0.731	*0.086*	0.511	1.045
Medium physical activity	0.537	*<0.001*	0.492	0.587	0.681	*0.008*	0.512	0.904
High physical activity	0.565	*<0.001*	0.511	0.624	0.647	*0.019*	0.449	0.931
2nd SIMD	0.797	*<0.001*	0.728	0.872	0.750	*0.082*	0.543	1.037
3rd SIMD	0.700	*<0.001*	0.636	0.771	1.022	*0.891*	0.749	1.394
4th SIMD	0.653	*<0.001*	0.591	0.721	0.922	*0.625*	0.666	1.277
5th SIMD (least deprived)	0.630	*<0.001*	0.566	0.702	0.752	*0.139*	0.516	1.097
Hospitalised last year	2.557	*<0.001*	2.300	2.843	1.387	*0.063*	0.983	1.956
Hospitalised over 1 year	1.590	*<0.001*	1.466	1.724	0.901	*0.432*	0.695	1.168
GHQ score (1-3)	1.298	*<0.001*	1.202	1.402	0.993	*0.961*	0.751	1.313
GHQ score (4+worse)	1.417	*<0.001*	1.299	1.546	1.686	*<0.001*	1.260	2.256
Constant	-3.919	*<0.001*	-4.105	-3.733	-9.991	*<0.001*	-10.823	-9.159
Gamma	-0.023	*<0.001*	-0.033	-0.014	0.045	*0.005*	0.013	0.076
Harrell's C-statistic	0.678				0.867			

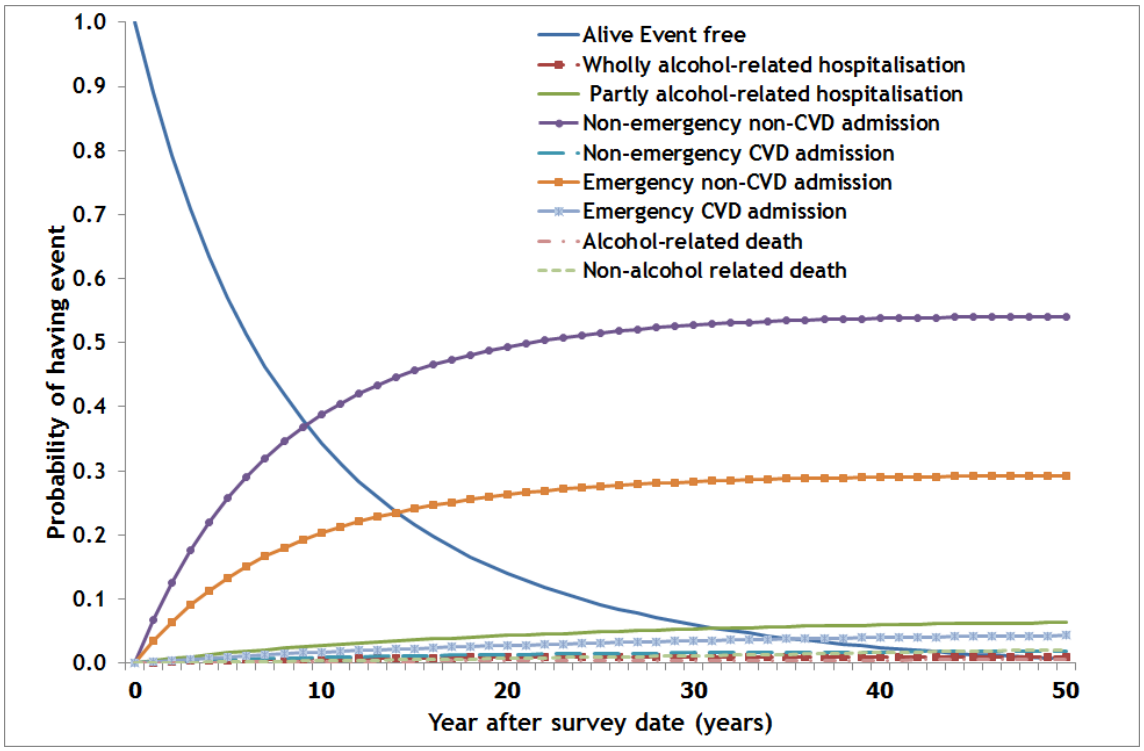
*Covariate reference: aged 16 years, AUDIT score=0, non-binge drinking, no CVD, no diabetes, non-smoking, no physical activity, most deprived (1st SIMD), no prior hospitalisation, and GHQ score=0 (best)

Table 6-7 Cause-specific hazards of non-alcohol related first event after survey date: females (cont.)

	c) non-emergency admission and non-CVD condition				d) non-emergency admission and CVD condition				e) Non-alcohol related death			
Covariate*	**Hazard ratio**	***p-value***	**95%CI**		**Hazard ratio**	***p-value***	**95%CI**		**Hazard ratio**	***p-value***	**95%CI**	
Age at survey date	1.013	*<0.001*	1.011	1.015	1.052	*<0.001*	1.037	1.066	1.109	*<0.001*	1.091	1.127
AUDIT score	0.997	*0.512*	0.988	1.006	0.948	*0.184*	0.875	1.026	0.987	*0.774*	0.901	1.081
Binge drinking	0.977	*0.533*	0.909	1.051	1.762	*0.053*	0.993	3.126	0.618	*0.255*	0.270	1.416
BMI (25-<30)	1.021	*0.467*	0.965	1.079	1.894	*0.006*	1.203	2.981				
BMI (>=30)	1.022	*0.526*	0.956	1.092	1.206	*0.467*	0.728	1.998				
having CVD	1.074	*0.013*	1.015	1.136	3.011	*<0.001*	2.041	4.441	1.226	*0.269*	0.855	1.759
having diabetes	1.114	*0.096*	0.981	1.264	1.756	*0.034*	1.044	2.952	1.836	*0.022*	1.091	3.088
Cigarettes per day	1.003	*0.027*	1.000	1.006	1.026	*0.008*	1.007	1.045	1.053	*<0.001*	1.037	1.069
Low activity	1.060	*0.202*	0.969	1.160	1.109	*0.702*	0.653	1.882	0.434	*0.006*	0.238	0.790
Medium activity	1.069	*0.066*	0.996	1.149	0.984	*0.943*	0.632	1.532	0.542	*0.004*	0.356	0.827
High activity	0.990	*0.797*	0.915	1.071	0.937	*0.813*	0.545	1.610	0.291	*0.001*	0.144	0.590
2nd	0.918	*0.016*	0.856	0.984	1.278	*0.303*	0.801	2.039	0.947	*0.805*	0.611	1.466
3rd	0.959	*0.241*	0.894	1.029	0.755	*0.311*	0.438	1.301	0.791	*0.339*	0.488	1.280
4th	0.866	*<0.001*	0.805	0.931	0.640	*0.132*	0.358	1.144	0.939	*0.795*	0.581	1.516
5th (least deprived)	0.817	*<0.001*	0.756	0.883	1.506	*0.109*	0.913	2.483	0.433	*0.015*	0.221	0.848
within last year	2.798	*<0.001*	2.596	3.015	2.099	*0.007*	1.225	3.597	1.663	*0.091*	0.922	2.999
over 1 year	1.616	*<0.001*	1.528	1.709	1.336	*0.178*	0.876	2.036	1.712	*0.017*	1.100	2.664
GHQ score (1-3)	1.208	*<0.001*	1.143	1.277	0.739	*0.171*	0.480	1.139	1.086	*0.684*	0.729	1.620
GHQ score (4+worse)	1.365	*<0.001*	1.281	1.455	1.262	*0.296*	0.815	1.953	1.162	*0.542*	0.716	1.885
Constant	-3.717	*<0.001*	-3.856	-3.578	-10.435	*<0.001*	-11.643	-9.228	-13.158	*<0.001*	-14.574	-11.742
Gamma	-0.035	*<0.001*	-0.041	-0.028	-0.026	*0.351*	-0.080	0.029	0.115	*<0.001*	0.067	0.162
Harrell's C-statistic	0.632				0.849				0.919			

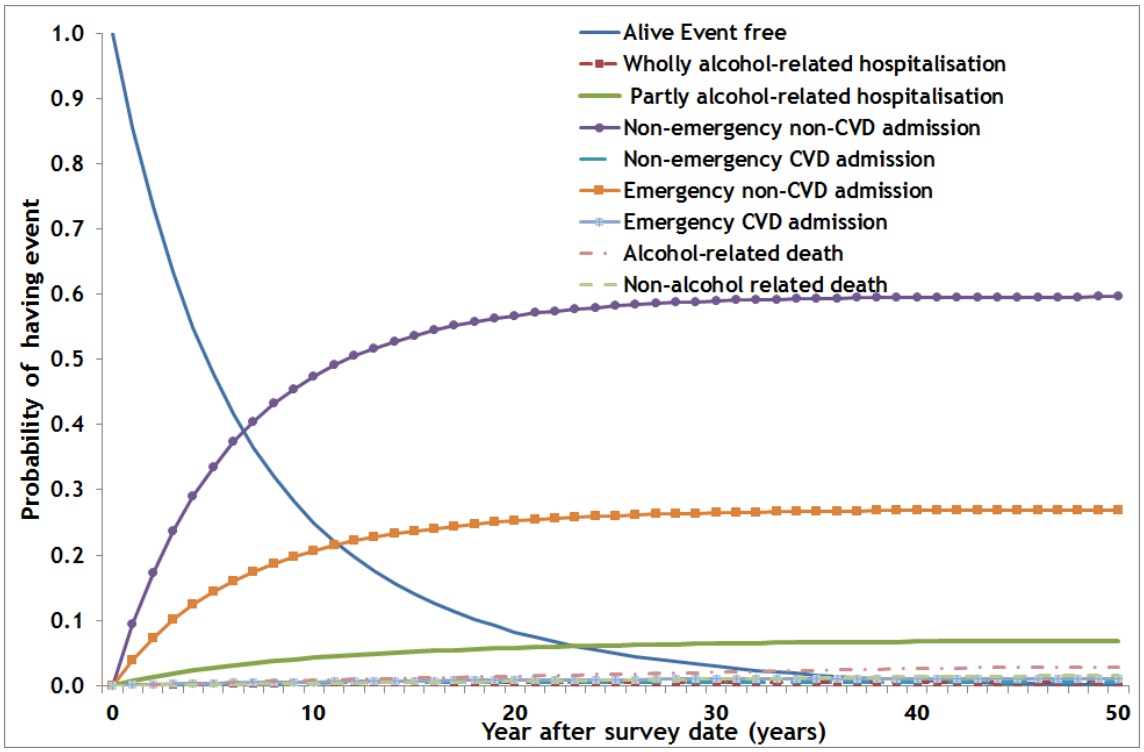
*Covariate reference: aged 16 years, AUDIT score=0, non-binge drinking, no CVD, no diabetes, non-smoking, no physical activity, most deprived (1st SIMD), no prior hospitalisation, and GHQ score=0 (best)

Figure 6-5 Predicted cumulative incidence of first events: males*



*Risk profiles: males, aged 30 years, AUDIT score=10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score

Figure 6-6 Predicted cumulative incidence of first events: females*



*Risk profiles: females, aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score

Table 6-8 Comparison of observed and predicted first alcohol-related events: males

Quintile of linear predictors	Number of events						*p*-value
	a) wholly alcohol-related hospitalisation		b) partly alcohol-related hospitalisation		c) alcohol-related death		
	Observed	Predicted	Observed	Predicted	Observed	Predicted	
1st (lowest risk)	3	3	11	18	2	2	*0.423*
2nd	1	4	31	35	3	4	*0.094*
3rd	5	6	65	58	5	5	*0.510*
4th	9	10	101	92	10	8	*0.377*
5th (highest risk)	33	28	133	138	18	19	*0.919*

Table 6-9 Comparison of observed and predicted first alcohol-related events: females

Quintile of linear predictors	Number of events						*p*-value
	a) wholly alcohol-related hospitalisation		b) partly alcohol-related hospitalisation		c) alcohol-related death		
	Observed	Predicted	Observed	Predicted	Observed	Predicted	
1st (lowest risk)	2	2	53	54	0	0	*0.423*
2nd	1	3	83	78	3	1	*0.497*
3rd	3	4	87	98	3	3	*0.373*
4th	10	6	137	129	6	7	*0.294*
5th (highest risk)	16	17	142	143	19	19	*0.183*

Table 6-10 Comparison of observed and predicted first non-alcohol related events: males

Quintile of linear predictors	Number of events					
	a) emergency admission and non-CVD condition		b) emergency admission and CVD condition		c) non-emergency admission and non-CVD condition	
	Observed	Predicted	Observed	Predicted	Observed	Predicted
1st (lowest risk)	376	348	4	13	620	609
2nd	406	409	19	28	708	754
3rd	473	480	61	53	874	852
4th	495	529	121	106	958	965
5th (highest risk)	672	656	214	219	1,142	1,123

Quintile of linear predictors	Number of events				*p*-value
	d) non-emergency admission and CVD condition		e) non-alcohol related death		
	Observed	Predicted	Observed	Predicted	
1st (lowest risk)	1	8	0	1	*0.556*
2nd	13	15	6	4	*0.257*
3rd	27	27	6	10	*0.505*
4th	60	49	28	24	*0.815*
5th (highest risk)	110	113	91	92	*0.364*

Table 6-11 Comparison of observed and predicted first non-alcohol related events: females

Quintile of linear predictors	Number of events					
	a) emergency admission and non-CVD condition		b) emergency admission and CVD condition		c) non-emergency admission and non-CVD condition	
	Observed	Predicted	Observed	Predicted	Observed	Predicted
1st (lowest risk)	377	337	3	4	874	862
2nd	438	424	8	11	1,074	1,031
3rd	504	518	23	25	1,085	1,147
4th	600	642	66	61	1,324	1,326
5th (highest risk)	982	981	169	168	1,506	1,497

Quintile of linear predictors	Number of events				*p*-value
	d) non-emergency admission and CVD condition		e) non-alcohol related death		
	Observed	Predicted	Observed	Predicted	
1st (lowest risk)	0	2	2	1	*0.275*
2nd	5	5	0	2	*0.298*
3rd	11	11	5	6	*0.253*
4th	35	26	17	19	*0.523*
5th (highest risk)	68	75	74	71	*0.614*

6.3.4 Modelling stage II: Survival following hospitalisation

The hazard ratios (HRs) of all-cause deaths after the first hospitalisation (i.e. alcohol-related and non-alcohol related condition) are shown in Table 6-12 and Table 6-13 for males and females, respectively. All cause-specific hazard ratios were derived from a Gompertz regression and multiple imputation using chained equations. The non-modifiable risk factors selected were age at the first hospitalisation, CVD condition, diabetes, and SIMD quintile. When other covariates were adjusted, HR values for males for a one-year increase in age at first hospitalisation were 1.047 (95% CI [1.032, 1.062], p<0.001) for death following alcohol-related hospitalisation, and 1.084 (95% CI [1.079, 1.089], p<0.001) for death following non-alcohol related hospitalisation. HR values for females were slightly higher than males at 1.064 (95% CI [1.049, 1.079], p<0.001) for death following alcohol-related hospitalisation, and 1.090 (95% CI [1.085, 1.095], p<0.001) for death following non-alcohol related hospitalisation. CVD and diabetes conditions were shown to increase the risk of death, particularly post non-alcohol related hospitalisation. For males, HR values were 1.193 (95% CI [1.058, 1.346], p=0.004) for CVD, and 1.564 (95% CI [1.309, 1.868], p<0.001) for diabetes. For females, HR values were 1.327 (95% CI [1.183, 1.488], p<0.001) for CVD, and 1.274 (95% CI [1.058, 1.535], p=0.011) for diabetes.

Compared with most deprivation (1st SIMD quintile), less deprivation (2nd to 5th SIMD quintiles) was shown to have protective effects from all-cause deaths following non-alcohol related hospitalisation in both males and females with a significant level of p<0.001. Less deprivation was seen reducing risk between 26% and 50% for all-cause death for males and 38% and 62% less risk of death for females. For all-cause death following alcohol-related hospitalisation, less deprivation was not statistically significant in terms of increasing death risk. In addition, the shape parameter (gamma) of the Gompertz model was shown to increase hazard over time (gamma=0.041, p<0.001 for males and 0.020, p=0.01 for females) for only all-cause death post non-alcohol related hospitalisation.

Figure 6-7 to Figure 6-10 present the Kaplan-Meier graphs of observed survival after first alcohol-related and non-alcohol related hospitalisations over the 20-year follow-up period, classified by gender. The graphs revealed that survival for males after alcohol-related hospitalisation were lower than non-alcohol related hospitalization with survival at 55% versus 75%, respectively. For females, survivals were likely similar when comparing between survival between alcohol-related and non-alcohol related hospitalisation.

To estimate the survival for the lifetime period, risk profiles were selected to predict survival after first hospitalisation beyond the follow-up period, classified by gender as shown in Figure 6-11 for males and Figure 6-12 for females. The selected risk profile was aged 35 at the time of the first event, no CVD, no diabetes, and 3rd SIMD. The predicted survival curves showed that survival following alcohol-related hospitalisation is seen to be lower than the survival following non-alcohol related admission over time. However, the predicted survival curves showed long tails due to the limited follow-up period so the linear predictors of survival models would need to be adjusted by calibration factors derived from the Scottish life table (National Records of Scotland, 2014). The adjusted survival curves are shown in the following section.

6.3.5 Assessment of model performance for predicting survival after first hospitalisation

Model discrimination of survival after first hospitalisation

Harrell's C–statistic of the survival models are shown in Table 6-12 and Table 6-13 classified by gender and first hospitalisation. Harrell's C–statistic values of models for death following alcohol-related hospitalisation were 0.68 and 0.76 for males and females, respectively. The C-statistic of models for death following non-alcohol related hospitalisation were better at predicting discrimination than the previous models, at 0.81 for males and 0.84 for females.

Internal validity of predicting survival post hospitalisation

The survival model was internally validated by comparing between the number of predicted and observed deaths across the linear predictor quintile (e.g. the highest fifth of linear predictors are those at highest risk). Table 6-14 and Table 6-15 present the comparison between observed and predicted mortality following alcohol-related and non-alcohol related hospitalisations for males and females, respectively. Then, a pair t-test was used to determine whether there was a difference in the number of predicted deaths compared with observed deaths across the risk quintile. As the p-values are more than 0.05 across all quintiles, it can be concluded that there was no difference in the number of predicted deaths compared with observed death.

Calibration model predictors using Scottish life table

Even though the model performed well for predicting first events and death following first events as shown in the internal validation, the model was not as good at predicting life expectancy as can be seen by the long tail survival curves. Thus, predicted life expectancies were compared with the Scottish life table (National Records of Scotland, 2014). Then, the calibration factors (gender-specific value) were calculated for adjusting the linear predictors of models. This analysis applied a squared-error loss function (corresponding to the root mean square error, or RMSE) as shown in the formula below:

$$RMSE^j = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(LE_i - \widehat{LE}_i^j)^2}$$

where LE_i is the Scottish life expectancy for the most and least deprivation of different ages, and $\widehat{LE}_i^j$ is the predicted life expectancy for j alternative multiplying factors which can minimise the RMSE. The selected multiplying factor is then applied to the linear predictor adjusting across all risk profiles. The results of calibration model predictors are presented in Table 6-16 and Table 6-17. For males, the multiplying factor was 0.88 and was applied across the linear predictors of the first event models and death after first

hospitalisation models. The overall RMSEs of different age were 2.19 years and 1.98 years for the most and least deprivation, respectively. For females, the different calibration factors of the predicting hospitalisation models and death models were 0.88 and 0.74, respectively. The overall RMSEs were 4.62 years for the most deprivation and 4.66 years for the least deprivation.

Figure 6-7 Observed survival after alcohol-related hospitalisation: males

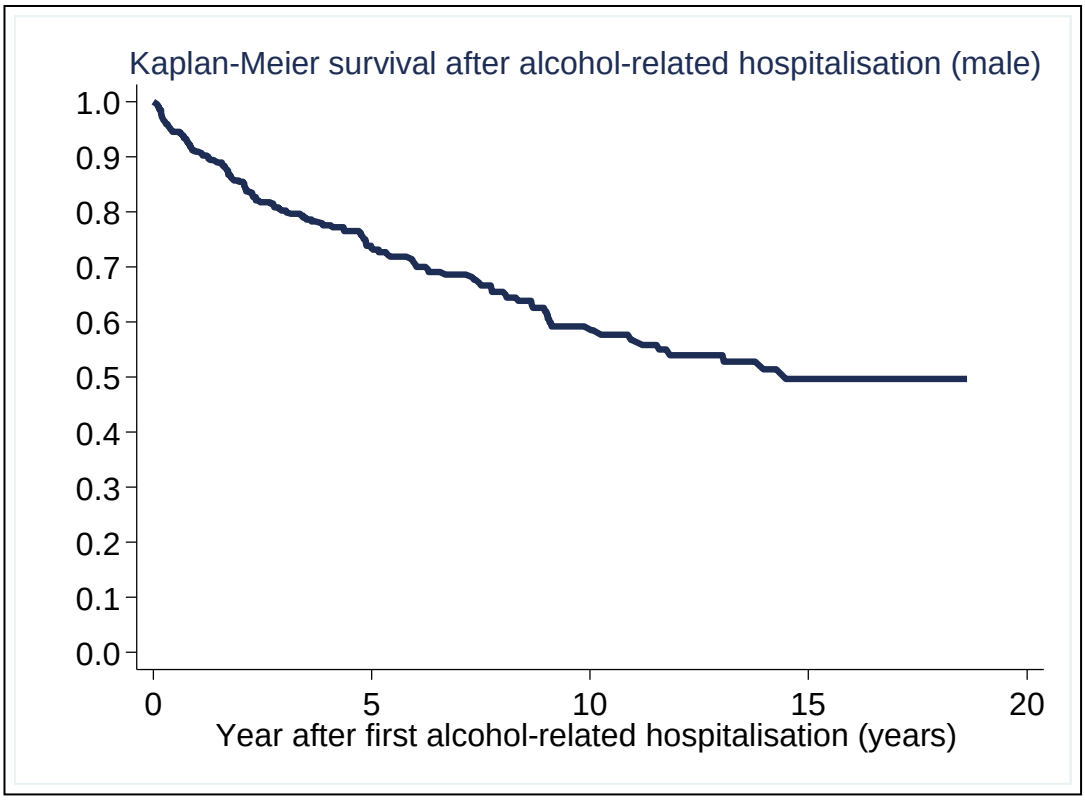


Figure 6-8 Observed survival after alcohol-related hospitalisation: females

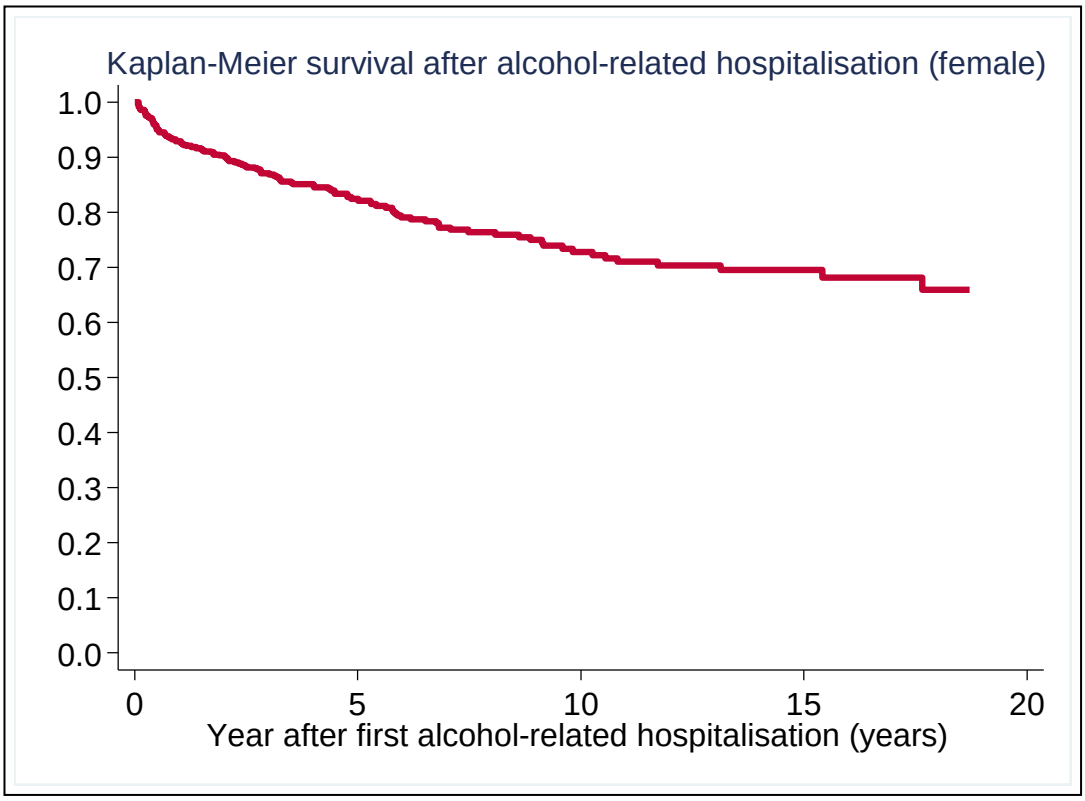


Figure 6-9 Observed survival after non-alcohol related hospitalisation: males

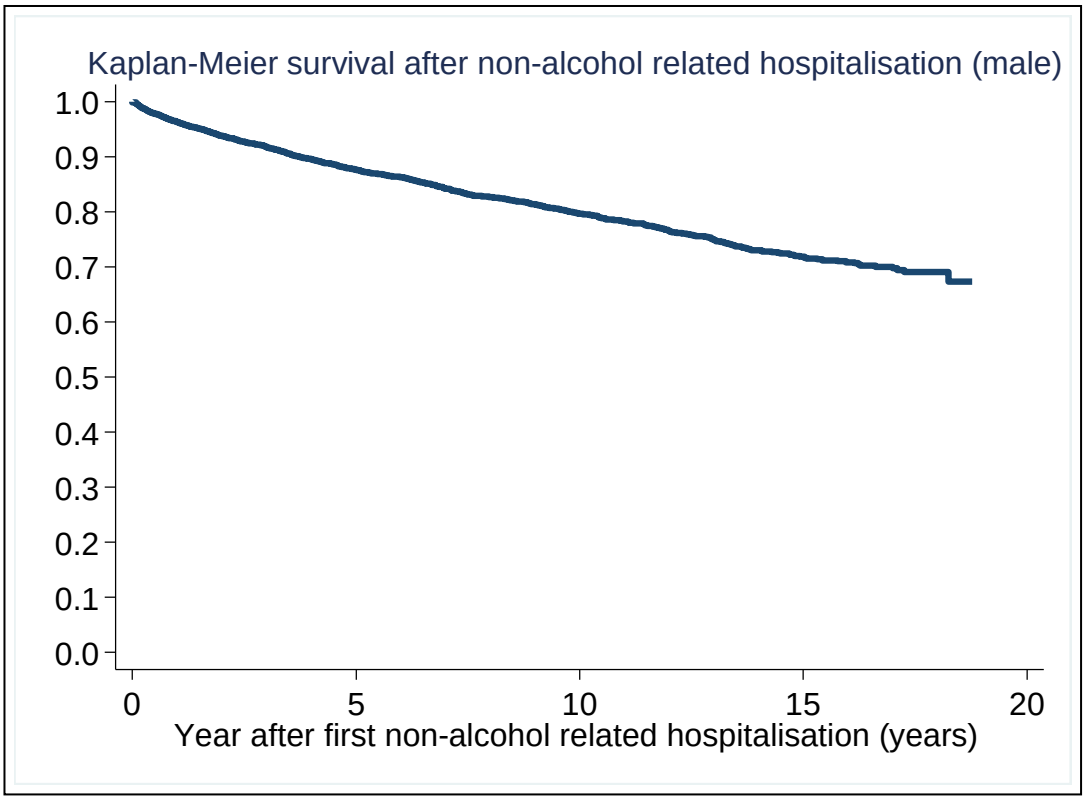


Figure 6-10 Observed survival after non-alcohol related hospitalisation: females

Table 6-12 Cause-specific hazards of all-cause death following first hospitalisation: males

	a) death following alcohol-related hospitalisation				b) death following non-alcohol related hospitalisation			
Covariate*	**Hazard ratio**	***p-value***	**95%CI**		**Hazard ratio**	***p-value***	**95%CI**	
Age at first hospitalisation	1.047	*<0.001*	1.032	1.062	1.084	*<0.001*	1.079	1.089
CVD	1.232	*0.268*	0.852	1.783	1.193	0.004	1.058	1.346
Diabetes	0.746	*0.464*	0.341	1.635	1.564	*<0.001*	1.309	1.868
2nd SIMD	0.463	*0.005*	0.270	0.795	0.842	0.025	0.724	0.979
3rd SIMD	0.562	*0.020*	0.347	0.913	0.630	*<0.001*	0.534	0.742
4th SIMD	0.741	*0.292*	0.424	1.294	0.604	*<0.001*	0.511	0.714
5th SIMD (least deprived)	0.649	*0.109*	0.383	1.101	0.501	*<0.001*	0.414	0.607
Constant	-5.200	*<0.001*	-6.190	-4.211	-8.498	*<0.001*	-8.847	-8.149
Gamma	-0.030	*0.291*	-0.086	0.026	0.041	*<0.001*	0.026	0.057
Harrell's C-statistic	0.678				0.808			

*****Covariate reference: aged 16 years, no CVD, no diabetes, and most deprived (1st SIMD)

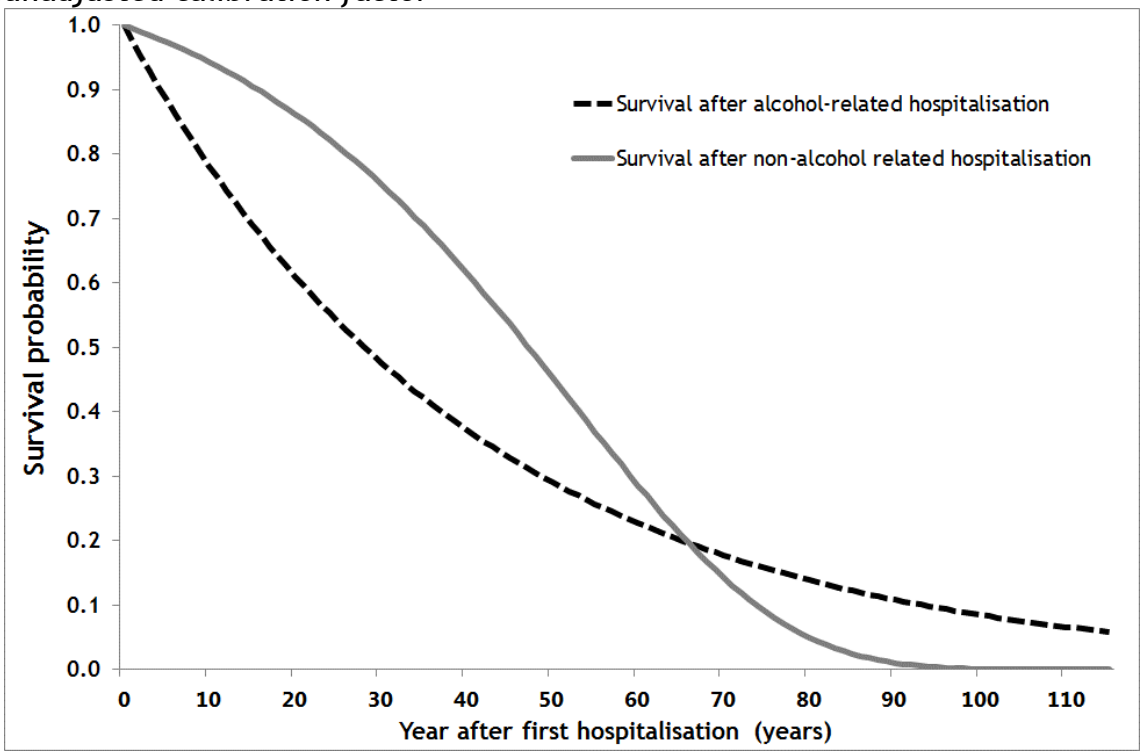
Table 6-13 Cause-specific hazards of all-cause death following first hospitalisation: females

	a) death following alcohol-related hospitalisation				b) death following non-alcohol related hospitalisation			
Covariate*	**Hazard ratio**	***p-value***	**95%CI**		**Hazard ratio**	***p-value***	**95%CI**	
Age at first hospitalisation	1.064	*<0.001*	1.049	1.079	1.090	*<0.001*	1.085	1.095
CVD	1.260	*0.262*	0.842	1.885	1.327	*<0.001*	1.183	1.488
Diabetes	0.683	*0.418*	0.271	1.720	1.274	*0.011*	1.058	1.535
2nd SIMD	1.001	*0.996*	0.574	1.746	0.617	*<0.001*	0.535	0.711
3rd SIMD	1.281	*0.341*	0.769	2.133	0.557	*<0.001*	0.479	0.648
4th SIMD	0.841	*0.576*	0.459	1.541	0.536	*<0.001*	0.458	0.626
5th SIMD (least deprived)	0.749	*0.351*	0.408	1.375	0.381	*<0.001*	0.314	0.462
Constant	-6.985	*<0.001*	-8.047	-5.924	-8.927	*<0.001*	-9.271	-8.582
Gamma	-0.050	*0.101*	-0.110	0.010	0.020	*0.010*	0.005	0.035
Harrell's C-statistic	0.764				0.840			

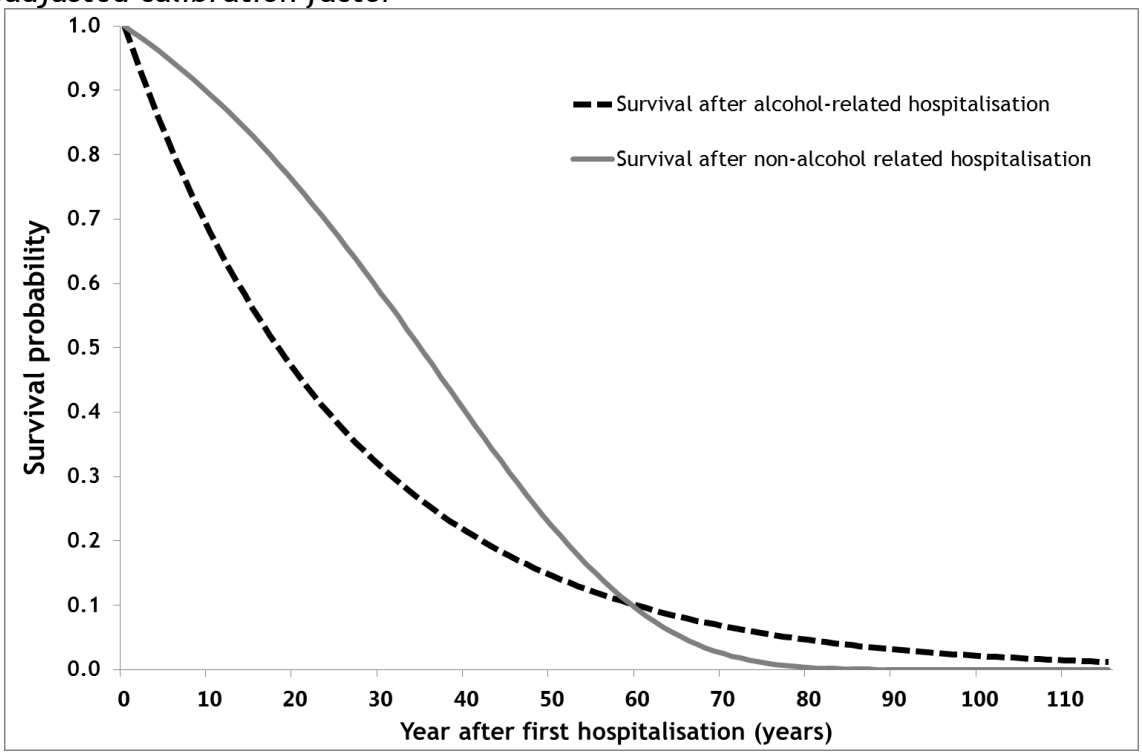
*****Covariate reference: aged 16 years, no CVD, no diabetes, and most deprived (1st SIMD)

Figure 6-11 Predicted survival after first hospitalisation: males*

i.unadjusted calibration factor



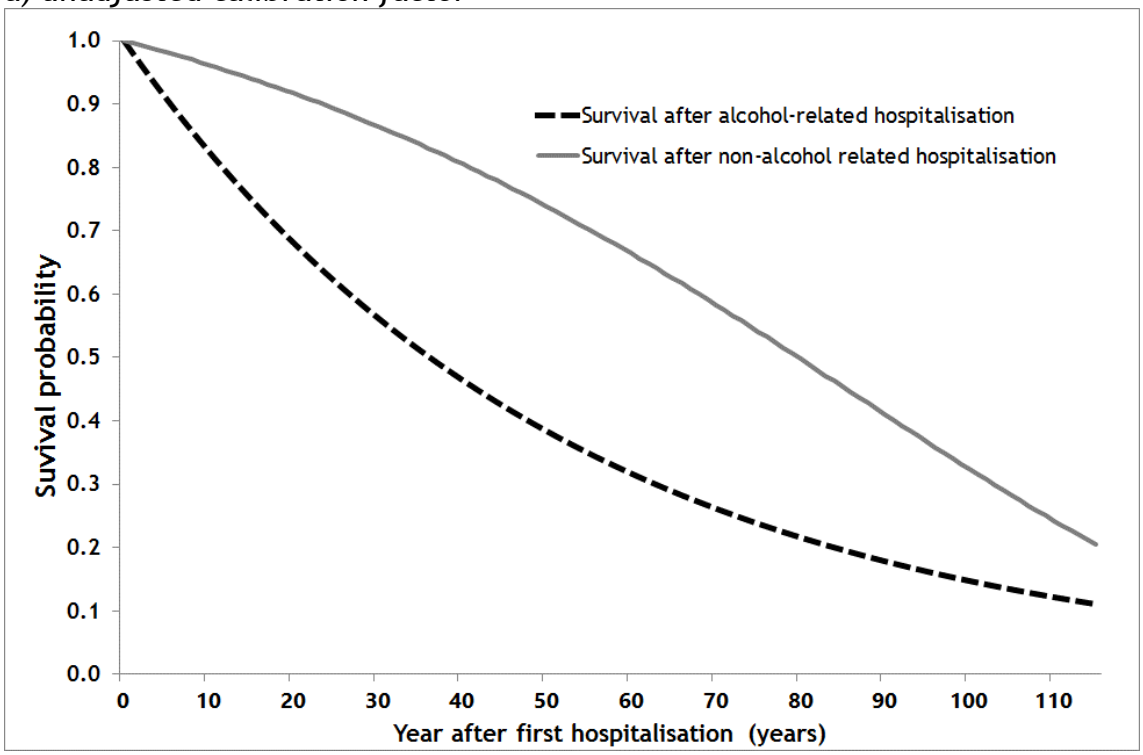
*ii.adjusted calibration factor***



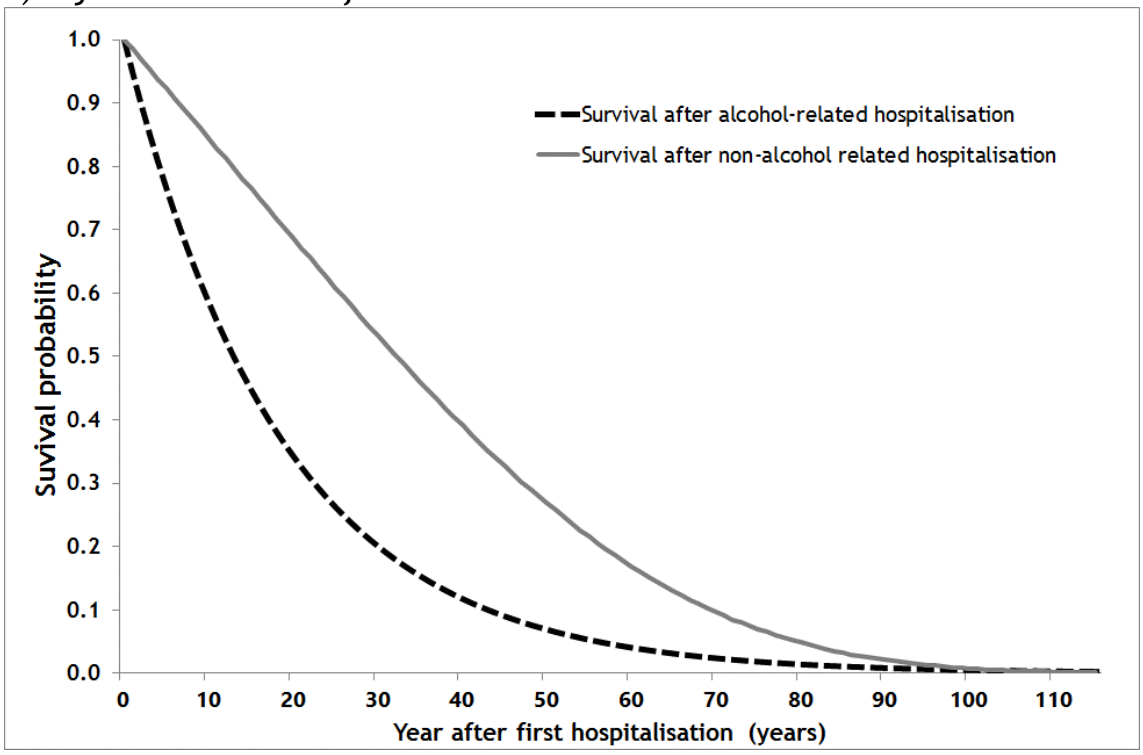
*Risk profiles: males, aged 45 at first event, no CVD, no diabetes, and 3rd SIMD
** The multiplying factor was 0.88 which was applied across the linear predictor of the first event models and death after first hospitalisation models.

Figure 6-12 Predicted survival after first hospitalisation: females*

a) unadjusted calibration factor



*b) adjusted calibration factor***



*Risk profiles: females, aged 45 at first event, no CVD, no diabetes, and 3rd SIMD
**The different calibration factors of the predicting hospitalisation models and death models were 0.88 and 0.74, respectively.

Table 6-14 Comparison of observed and predicted death following first hospitalisation events: males

Quintile of linear predictors	Number of events				*p* value
	a) death post alcohol-related hospitalisation		b) death post non-alcohol related hospitalisation		
	Observed	Predicted	Observed	Predicted	
1st (lowest risk)	12	13	29	33	*0.344*
2nd	18	19	85	84	*1.000*
3rd	28	29	197	203	*0.395*
4th	38	34	379	371	*0.205*
5th (highest risk)	37	37	601	600	*0.500*

Table 6-15 Comparison of observed and predicted death following first hospitalisation events: females

Quintile of linear predictors	Number of events				*p* value
	a) death post alcohol-related hospitalisation		b) death post non-alcohol related hospitalisation		
	Observed	Predicted	Observed	Predicted	
1st (lowest risk)	2	6	29	22	*0.831*
2nd	12	12	63	59	*0.500*
3rd	22	21	176	166	*0.437*
4th	31	31	370	409	*0.500*
5th (highest risk)	51	49	776	758	*0.430*

Table 6-16 Calibration model predictors using the Scottish life table: males

Age	Life expectancy (years)					
	Scottish life table		Model prediction (Unadjusted linear predictor)		Model prediction (Multiplied linear predictor)*	
(years)	Most deprivation	Least deprivation	Most deprivation	Least deprivation	Most deprivation	Least deprivation
20	70.65	82.79	89.19	100.25	76.40	87.34
25	70.99	82.86	87.26	98.72	75.19	85.86
30	71.45	82.97	85.40	96.87	74.24	84.52
35	72.04	83.1	83.77	95.02	73.55	83.36
40	72.84	83.23	82.37	93.20	73.24	82.41
45	73.81	83.4	81.33	91.59	73.32	81.81
50	74.83	83.67	80.72	90.26	73.83	81.56
55	76.05	84.00	80.59	89.31	74.82	81.72
60	77.56	84.52	81.01	88.82	76.29	82.35
65	79.36	85.23	82.01	88.82	78.22	83.45
70	81.38	86.19	83.59	89.39	80.64	85.03
75	83.95	87.60	85.73	90.54	83.47	87.11
80	86.88	89.44	88.38	92.28	86.71	89.65
85	90.22	92.04	91.49	94.57	90.26	92.60
RMSE			***9.16***	***9.24***	***2.19***	***1.98***

RMSE: Root mean square error

* The multiplying factor was 0.88 which was applied across the linear predictor of the first event models and death after first hospitalisation models.

Table 6-17 Calibration model predictors using the Scottish life table: females

Age	Life expectancy (years)					
	Scottish life table		Model prediction (Unadjusted linear predictor)		Model prediction (Multiplied linear predictor)*	
(years)	Most deprivation	Least deprivation	Most deprivation	Least deprivation	Most deprivation	Least deprivation
20	76.76	85.16	116.74	125.20	80.94	96.05
25	76.88	85.19	114.80	125.91	77.98	93.63
30	77.02	85.26	111.58	125.52	75.40	90.88
35	77.36	85.31	107.14	123.95	73.40	88.11
40	77.79	85.42	101.98	121.12	72.16	85.61
45	78.23	85.54	96.75	117.10	71.67	83.71
50	78.86	85.75	92.17	112.34	71.96	82.50
55	79.70	86.11	88.72	107.37	72.97	82.03
60	80.73	86.50	86.57	102.95	74.63	82.29
65	82.06	87.07	85.73	99.51	76.86	83.26
70	83.64	87.79	86.05	97.32	79.60	84.86
75	85.69	88.85	87.40	96.37	82.77	87.04
80	88.26	90.29	89.59	96.59	86.30	89.74
85	91.15	92.31	92.44	97.81	90.10	92.84
RMSE			***9.85***	***10.52***	***4.62***	***4.66***

RMSE: Root mean square error

* The different calibration factors of the predicting hospitalisation models and death models were 0.88 and 0.74, respectively.

6.3.6 Modelling stage III: Estimating life years

Table 6-18 (a-c) and Table 6-19 (a-c) demonstrate the three stages of estimating the overall life expectancy of individual risk profiles for males and females aged 30 years, respectively. Table 6-18a and Table 6-19a represent the first stage which is the sum of the survival time before the events and the survival time following the first hospitalisation for 100 annual cycles. For example, if the individual risk profile of males aged 30 years had a wholly alcohol-related hospitalisation in the first year (first cycle) after the survey date, the remaining LYs would be 44.4 years; this figure comprised a survival time of one year before having the event and a remaining survival time of 43.4 years following the hospitalisation. Table 6-18b and Table 6-19b show the probabilities of having 8 first events across 100 annual cycles derived from the cause-specific hazard model of a particular risk profile as defined. Finally, the remaining LYs of each health state (Table 6-18a and Table 6-19a) were weighted by the probabilities of having a particular event (Table 6-18b and Table 6-19b), resulting in the predicted additional LYs after the survey date as shown in Table 6-18c and Table 6-19c. Thus, the estimated overall life expectancies of the defined risk profiles were 81.54 years and 84.27 years for males and females, respectively.

To demonstrate the use of the model for predicting the LYs, the selected risk profiles were varied by age, group AUDIT score, smoking status and SIMD quintile. Subsequently, the predicted life expectancies of these risk profiles are illustrated in Table 6-20 and Table 6-21 for males and females, respectively. The model shows its ability to discriminate between risk profiles as presented by different life expectancies for both males and females. The results revealed that higher-risk drinking (higher AUDIT score), more deprived status and current smoker reduced life expectancies when other related risk profiles were also changed based on the characteristics of the study population.

Table 6-18 Estimating life years using 3 stages: males*

a) Life years remaining upon entering model (for hospitalisation, life year is equal to time before event added with the time remaining after event)

Cycle (years)	Wholly alcohol-related hospitalisation	Partly alcohol-related hospitalisation	Non-emergency non-CVD admission	Non-emergency CVD admission	Emergency non-CVD admission	Emergency CVD admission	Alcohol-related death	Non-alcohol related death
1	44.4	44.4	55.4	55.4	55.4	55.4	1.0	1.0
2	44.1	44.1	54.9	54.9	54.9	54.9	2.0	2.0
3	43.8	43.8	54.5	54.5	54.5	54.5	3.0	3.0
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
22	42.3	42.3	50.0	50.0	50.0	50.0	22.0	22.0
23	42.5	42.5	49.9	49.9	49.9	49.9	23.0	23.0
24	42.7	42.7	49.9	49.9	49.9	49.9	24.0	24.0
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
100	101.0	101.0	100.5	100.5	100.5	100.5	100.0	100.0

*Risk profiles: males, aged 30 years, AUDIT score=10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score

Table 6-18 Estimating life year using 3 stages: males* (cont.)

b) Probability of having 8 events over 100 annual cycles

Cycle (years)	Wholly alcohol-related hospitalisation	Partly alcohol-related hospitalisation	Non-emergency non-CVD admission	Non-emergency CVD admission	Emergency non-CVD admission	Emergency CVD admission	Alcohol-related death	Non-alcohol related death
1	0.0012	0.0037	0.0674	0.0013	0.0343	0.0022	0.0003	0.0004
2	0.0011	0.0034	0.0582	0.0012	0.0299	0.0021	0.0003	0.0004
3	0.0009	0.0032	0.0504	0.0011	0.0261	0.0019	0.0003	0.0004
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
22	0.0001	0.0012	0.0047	0.0003	0.0028	0.0008	0.0001	0.0004
23	0.0001	0.0011	0.0042	0.0003	0.0025	0.0008	0.0001	0.0004
24	0.0001	0.0011	0.0037	0.0003	0.0023	0.0008	0.0001	0.0004
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
100	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

*Risk profiles: males, aged 30 years, AUDIT score=10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score

Table 6-18 Estimating life year using 3 stages: males* (cont.)

c) Weighting remaining life years estimated from stage a) multiplied by stage b)

Cycle (years)	Wholly alcohol-related hospitalisation	Partly alcohol-related hospitalisation	Non-emergency non-CVD admission	Non-emergency CVD admission	Emergency non-CVD admission	Emergency CVD admission	Alcohol-related death	Non-alcohol related death	***Sum***
1	0.0546	0.1627	3.7308	0.0701	1.9002	0.1226	0.0003	0.0004	**6.0417**
2	0.0466	0.1498	3.1980	0.0637	1.6414	0.1138	0.0006	0.0008	**3.4582**
3	0.0399	0.1384	2.7489	0.0581	1.4218	0.1058	0.0008	0.0011	**2.9854**
.	.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.	.
22	0.0033	0.0488	0.2347	0.0150	0.1405	0.0406	0.0020	0.0087	**0.3019**
23	0.0030	0.0471	0.2094	0.0142	0.1263	0.0392	0.0020	0.0092	**0.2737**
24	0.0027	0.0455	0.1870	0.0134	0.1137	0.0379	0.0020	0.0098	**0.2486**
.	.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.	.
100	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	**0.0000**

*Risk profiles: males, aged 30 years, AUDIT score=10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score

Total life years remaining (Cumulative sum over 100 cycles) = 51.54

Overall life expectancy (age upon entering model plus remaining life years) = 81.54

Table 6-19 Estimating life year using 3 stages: females*

a) Life year remaining upon entering model (for hospitalisation, life year is equal to time before event added with the time remaining after event)

Cycle (years)	Wholly alcohol-related hospitalisation	Partly alcohol-related hospitalisation	Non-emergency non-CVD admission	Non-emergency CVD admission	Emergency non-CVD admission	Emergency CVD admission	Alcohol-related death	Non-alcohol related death
1	36.4	36.4	61.7	61.7	61.7	61.7	1.0	1.0
2	36.0	36.0	60.9	60.9	60.9	60.9	2.0	2.0
3	35.7	35.7	60.0	60.0	60.0	60.0	3.0	3.0
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
22	36.2	36.2	49.6	49.6	49.6	49.6	22.0	22.0
23	36.6	36.6	49.4	49.4	49.4	49.4	23.0	23.0
24	36.9	36.9	49.2	49.2	49.2	49.2	24.0	24.0
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
100	100.6	100.6	100.5	100.5	100.5	100.5	100.0	100.0

*Risk profiles: females, aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score

Table 6-19 Estimating life year using 3 stages: females* (cont.)

b) Probability of having 8 events over 100 annual cycles

Cycle (years)	Wholly alcohol-related hospitalisation	Partly alcohol-related hospitalisation	Non-emergency non-CVD admission	Non-emergency CVD admission	Emergency non-CVD admission	Emergency CVD admission	Alcohol-related death	Non-alcohol related death
1	0.0009	0.0070	0.0942	0.0008	0.0397	0.0009	0.0010	0.0004
2	0.0007	0.0061	0.0778	0.0007	0.0332	0.0008	0.0010	0.0004
3	0.0006	0.0054	0.0646	0.0006	0.0278	0.0007	0.0009	0.0004
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
22	0.0000	0.0009	0.0034	0.0000	0.0018	0.0002	0.0006	0.0003
23	0.0000	0.0008	0.0029	0.0000	0.0016	0.0002	0.0006	0.0003
24	0.0000	0.0007	0.0026	0.0000	0.0014	0.0002	0.0006	0.0003
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
100	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

*Risk profiles: females, aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score

Table 6-19 Estimating life year using 3 stages: females* (cont.)

c) Weighting remaining life years estimated from stage a) multiplied by stage b)

Cycle (years)	Wholly alcohol-related hospitalisation	Partly alcohol-related hospitalisation	Non-emergency non-CVD admission	Non-emergency CVD admission	Emergency non-CVD admission	Emergency CVD admission	Alcohol-related death	Non-alcohol related death	***Sum***
1	0.0320	0.2543	5.8092	0.0490	2.4478	0.0547	0.0010	0.0004	**8.6484**
2	0.0263	0.2205	4.7347	0.0403	2.0177	0.0483	0.0019	0.0008	**5.0217**
3	0.0217	0.1921	3.8759	0.0333	1.6705	0.0428	0.0027	0.0011	**4.1230**
.	.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.	.
22	0.0013	0.0311	0.1675	0.0017	0.0895	0.0084	0.0134	0.0071	**0.2016**
23	0.0011	0.0291	0.1455	0.0015	0.0786	0.0079	0.0140	0.0075	**0.1772**
24	0.0010	0.0272	0.1266	0.0013	0.0692	0.0074	0.0145	0.0080	**0.1561**
.	.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.	.
100	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	**0.0000**

*Risk profiles: females, aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, Prior hospitalisation over last year, and best GHQ score

Total life years remaining (Cumulative sum over 100 cycles) = 54.27

Overall life expectancy (age upon entering model plus remaining life years) = 84.27

Table 6-20 Predicted life expectancies classified by risks profiles: males

AUDIT score	Smoker (5 CPD)					Non-smoker				
	Age 20 years					**Age 20 years**				
>20	75.03	79.46	83.81	83.83	86.32	75.18	79.48	83.85	83.91	86.40
16 - 19	75.96	79.81	84.04	84.37	86.88	76.04	79.83	84.06	84.43	86.97
8 - 15	76.12	79.87	84.08	84.47	86.98	76.20	79.90	84.11	84.52	87.03
0 - 7	76.40	79.99	84.12	84.60	87.16	76.47	80.02	84.15	84.69	87.21
	Age 30 years					**Age 30 years**				
>20	72.97	76.97	80.97	81.07	83.51	73.11	77.04	81.03	81.19	83.61
16 - 19	73.84	77.38	81.30	81.67	84.12	73.96	77.45	81.35	81.74	84.20
8 - 15	74.00	77.45	81.37	81.75	84.25	74.12	77.53	81.42	81.85	84.32
0 - 7	74.28	77.60	81.50	81.95	84.46	74.40	77.67	81.55	82.01	84.53
	Age 40 years					**Age 40 years**				
>20	72.14	75.57	79.04	79.23	81.43	72.28	75.64	79.15	79.34	81.57
16 - 19	72.93	76.01	79.47	79.80	82.07	73.03	76.07	79.54	79.89	82.18
8 - 15	73.08	76.10	79.53	79.92	82.20	73.18	76.16	79.63	80.00	82.31
0 - 7	73.36	76.23	79.69	80.11	82.43	73.45	76.32	79.76	80.21	82.51
	Age 50 years					**Age 50 years**				
>20	72.93	75.70	78.57	78.77	80.68	73.06	75.79	78.66	78.88	80.80
16 - 19	73.59	76.12	79.00	79.30	81.27	73.70	76.20	79.08	79.39	81.40
8 - 15	73.73	76.21	79.07	79.41	81.40	73.84	76.29	79.16	79.51	81.50
0 - 7	73.99	76.36	79.25	79.60	81.64	74.09	76.44	79.34	79.69	81.74
	1	2	3	4	5	1	2	3	4	5
	most deprived				least deprived	most deprived				least deprived
	SIMD quintile									

Note: binge drinking, BMI, physical activity, CVD, diabetes, prior hospitalisation, and GHQ score were varied but not presented.

Table 6-21 Predicted life expectancies classified by risks profiles: females

AUDIT score	Smoker (4 CPD)					Non-smoker				
	Age 20 years					Age 20 years				
>17	79.60	86.15	87.32	88.50	92.70	79.67	86.28	87.47	88.62	92.85
13 - 16	80.57	87.74	88.99	89.94	94.72	80.59	87.78	89.05	89.99	94.80
5 - 12	80.86	88.23	89.50	90.41	95.39	80.86	88.28	89.57	90.41	95.41
0 - 4	81.13	88.65	89.94	90.79	95.94	81.09	88.67	89.98	90.76	95.96
	Age 30 years					Age 30 years				
>17	74.02	80.57	81.84	83.11	87.81	74.14	80.74	82.03	83.28	88.00
13 - 16	74.83	81.91	83.24	84.31	89.59	74.90	82.01	83.38	84.41	89.68
5 - 12	75.07	82.33	83.68	84.71	90.14	75.13	82.43	83.79	84.76	90.24
0 - 4	75.28	82.68	84.05	84.99	90.65	75.33	82.75	84.14	85.06	90.68
	Age 40 years					Age 40 years				
>17	70.81	76.28	77.44	78.62	82.87	70.95	76.49	77.66	78.81	83.09
13 - 16	71.46	77.37	78.56	79.60	84.36	71.58	77.54	78.74	79.73	84.51
5 - 12	71.66	77.70	78.91	79.87	84.83	71.77	77.85	79.07	80.01	84.94
0 - 4	71.82	77.98	79.21	80.11	85.22	71.90	78.11	79.32	80.21	85.31
	Age 50 years					Age 50 years				
>17	70.72	74.84	75.78	76.76	80.08	70.91	75.07	76.01	76.98	80.36
13 - 16	71.24	75.69	76.65	77.50	81.27	71.37	75.87	76.83	77.68	81.48
5 - 12	71.39	75.95	76.92	77.70	81.64	71.52	76.11	77.08	77.89	81.80
0 - 4	71.49	76.14	77.12	77.88	81.95	71.61	76.31	77.27	78.04	82.09
	1	2	3	4	5	1	2	3	4	5
	most deprived				least deprived	most deprived				least deprived
	SIMD quintile									

Note: binge drinking, BMI, physical activity, CVD, diabetes, prior hospitalisation, and GHQ score were varied but not presented.

6.4 Discussion

This chapter described the stages of developing an alcohol intervention model including the conceptualisation of the model, the construction of the health state transition model, data source used (i.e. SHeS-SMR/NRS linkage data), adjusted under-reporting alcohol consumption and dealing with missing data among survey population, and statistical approach used for data modelling, model validation, and calibration using the Scottish life table. The analyses also incorporated the predicted AUDIT score. Then, the model utilisation for predicting LYs of different risk profiles were demonstrated and the results presented were classified by modifiable risk factors, i.e. drinking status as measured by the AUDIT (Babor et al., 2001, Babor et al., 1989) - which was predicted using an OLS regression as described in Chapter 4, binge drinking, and other selected behavioural risk factors (e.g. cigarettes per day, BMI, and physical activity). The results showed that the developed alcohol intervention model was able to predict the hospitalisation and death events of each individual risk profile; most of the models indicated good performance in terms of predictive discrimination (Harrell's C–statistic) and comparison between the number of predicted and observed events. However, the predicted overall life expectancies of different risks profiles were longer than the Scottish life table so the Scottish life expectancies were used to calibrate the model (National Records of Scotland, 2014). The predicted overall LYs of different drinking status can be used in the alcohol intervention model to monitor and evaluate the effectiveness of alcohol intervention in terms of morbidity and mortality. Furthermore, other modifiable behaviour risk factors were considered in the model.

This study is likely the first one that uses linkage data between health surveys and recorded hospitalisations and deaths to model the wide range of events of interest, i.e. alcohol-related conditions and all occurring non-alcohol related conditions within the follow-up period. Moreover, the modelling approach was applied to extrapolate the survival risk over the lifetime, and life

expectancy of different risk profile (including modifiable risk factors and socioeconomic status) was then estimated. The approaches used in this study can be used as a complimentary analysis to RCTs of an alcohol intervention, where effectiveness was estimated only for period of the study (Cowell et al., 2012, Crawford et al., 2014, Crawford et al., 2015, UKATT Research Team, 2005a). Therefore, this approach can be conducted to determine its effectiveness in terms of decreasing morbidity and mortality beyond study period.

This current modelling study is the first one to incorporate alcohol drinking patterns as measured by the AUDIT score to identify individual alcohol use disorder by accounting for the average level of alcohol consumption, heavy episodic drinking, and other alcohol-related harms. This is different from most of the previous modelling studies, e.g. the cost-effectiveness of screening and brief intervention (SBI) for alcohol use disorder (Barbosa et al., 2015, Cowell et al., 2010, Purshouse et al., 2013, Angus et al., 2014a) as well as meta-analyses (Bray et al., 2011, Donoghue et al., 2014, Fachini et al., 2012, Babor et al., 2007); these studies investigated changes of consumption and/or alcohol-related harms within the follow-up period, and the changes in consumption level were then modelled to estimate the changes of alcohol-related diseases and/or other harms over time. Moreover, previous existing alcohol models had a limited number of 'drinking states' from which to examine the distribution of consumption and alcohol-related problems within the cohort, e.g. absenteeism, moderate-risk, and high-risk consumptions (Barbosa et al., 2015, Barbosa et al., 2010b, Purshouse et al., 2013, Cobiac et al., 2009), leading to a limited range of drinking subgroups. However, the AUDIT score is able to classify a wider range of alcohol use disorders which may cause different alcohol-related problems and consequences.

Not only were the wide range of drinking states presented in the current model but other risk factors (i.e. health behaviours and socioeconomic status) were combined with the AUDIT score to capture the overall impact of combined

risk factors on morbidity and mortality as well. Therefore, the results derived from this analysis can be shown via various risk profiles. Many observational studies as well as meta-analyses have also shown an increasing shift from interest in only alcohol consumption and its harms to focussing on the effects of combined risk behaviours (included alcohol drinking) to diseases and mortality (Khaw et al., 2008, Kvaavik et al., 2010, Loef and Walach, 2012, Petersen et al., 2015, Tamakoshi et al., 2010, Yun et al., 2012, Carlsson et al., 2013, Klijs et al., 2011). According to methodological issues surrounding this analysis as mentioned above, the approach used for the current alcohol intervention model differed from other modelling studies so it would be difficult to directly compare with other alcohol intervention evaluation studies.

Moreover, the developed model focussed on the relationship between the selected modifiable risk factor and the risk of first events (i.e. hospitalisations and deaths). Thus, this model can be applied for the evaluation of primary prevention interventions which aim to reduce the risk of a first event of interest. Finally, the model was also calibrated using the Scottish life table to adjust the linear predictor so it likely has high internal validity but low external validity. In particular, a key component of the alcohol intervention model in the Scottish context was the indices of deprivation or SIMD quintile (Office of the Chief Statistician, 2004), and this is not measured in other countries. However, the linear predictor of the model can be recalibrated using country-specific life tables and SIMD quintiles as a covariate that can be replaced with other deprivation indices.

6.5 Conclusions

Long-term outcome measurements in alcohol intervention models and the evaluation of combined health risk behaviours is still scarce. The applicable approaches of this study would emphasise and recommend the use of routine national health surveys and national hospitalisation and death records as well as modelling morbidity and mortality of different combined modifiable risk profiles.

Chapter 7: The use of alcohol intervention model for predicting quality adjusted life years and lifetime hospitalisation costs

7.1 Introduction

Evaluation public health policy using a modelling approach has become increasingly applied to policy analyses which support the design of efficient and effective policy options for complex public health problems (Ashley et al., 2015, Atkinson et al., 2015, Brennan et al., 2014b). The economic evaluation of the alcohol policies has been applied for informing policy-decision makers at both population- and individual-levels interventions (Ashley et al., 2015, Barbosa et al., 2015, Barbosa et al., 2010b, Brennan et al., 2014a, Brennan et al., 2014b, Cadilhac et al., 2011, Chisholm et al., 2004, Galea et al., 2009, Holmes et al., 2014a, Marsh et al., 2012, Byrnes et al., 2010, Cobiac et al., 2009, Purshouse et al., 2013). Thus, the model analysis tool is able to test the interest effectiveness and cost-effectiveness through modelling the expected changes in modifiable risk factors caused by the intervention. Although RCTs are still the gold standard of obtaining a causal estimate of intervention effectiveness, there is a limited follow-up period for conducting a cost-effectiveness analysis alongside RCTs as well as RCTs would not be appropriate for large-scale public health interventions. Thus, modelling studies are often necessary to extrapolate longer term outcome in a lifetime horizon beyond the end of the trials (Kruger et al., 2014, Barbosa et al., 2010a, Alayli-Goebbels et al., 2014). For model-based economic evaluations, lifetime QALYs and costs are widely recommended for the purposes of the economic evaluation of healthcare interventions to inform policy decision-making (ISPOR, 2014, NICE, 2013, Chaikledkaew and Kittrongsiri, 2014, Teerawattananon and Chaikledkaew, 2008); these standard methods are also applied to public health interventions (Edwards et al., 2013, Weatherly et al., 2009).

This study used a modelling approach, namely the alcohol intervention model, to examine the selected risk profiles (e.g. alcohol drinking, smoking and

SIMD) and the predicted long-term consequences in terms of life expectancy (as illustrated in Chapter 6), QALYs, and lifetime hospitalisation costs. The estimated costs and outcomes can be used for further economic evaluations of an alcohol intervention which aims to modify selected individual risk behaviours. This chapter describes the use of the developed alcohol intervention model for predicting health outcome in terms of QALYs as well as lifetime hospitalisation cost of the different selected risk profiles. First, the relevant health state transition model was specified to model the QALYs and hospitalisation costs. Second, using the SHeS-SMR/NRS linked dataset, the data modelling for predicting QALYs was performed using three components: 1) the baseline HRQoL score and utility decrement due to hospitalisation and the increasing AUDIT score as described in Chapter 5; 2) the annual probability of having subsequent hospitalisation after the first admission; and 3) adjusting the HRQoL of each health state with the survival function as described in Chapter 6. Finally, based on the NHS perspective, the lifetime hospitalisation costs were modelled using three stages: 1) identifying the data source for cost analysis; 2) modelling annual hospitalisation costs since the year when the first event occurs; and 3) predicting life time hospitalisation costs. Furthermore, the results derived from the data model were compared to observed hospitalisation records (SMR 01; inpatients and day cases). Then, the estimated QALYs and lifetime healthcare costs were presented and classified by different individual risk profiles.

7.2 Methods

This study aimed to identify the first alcohol-related admissions (incident cases) and the following hospital admissions both alcohol and non-alcohol related conditions identified by ICD-9/ICD-10 (Appendix 1). Then, the associated healthcare costs and outcomes (i.e. life years and QALYs) for all individuals hospitalised were estimated and compared between health risk profiles classified by age, sex, risk behaviours (e.g. drinking and smoking), SIMD, and health conditions (e.g. CVD and DM). Individuals SHeS participants, who had hospital admissions, were derived from the SMR01, which is national data schemes that record comprehensive information including diagnoses (ICD-

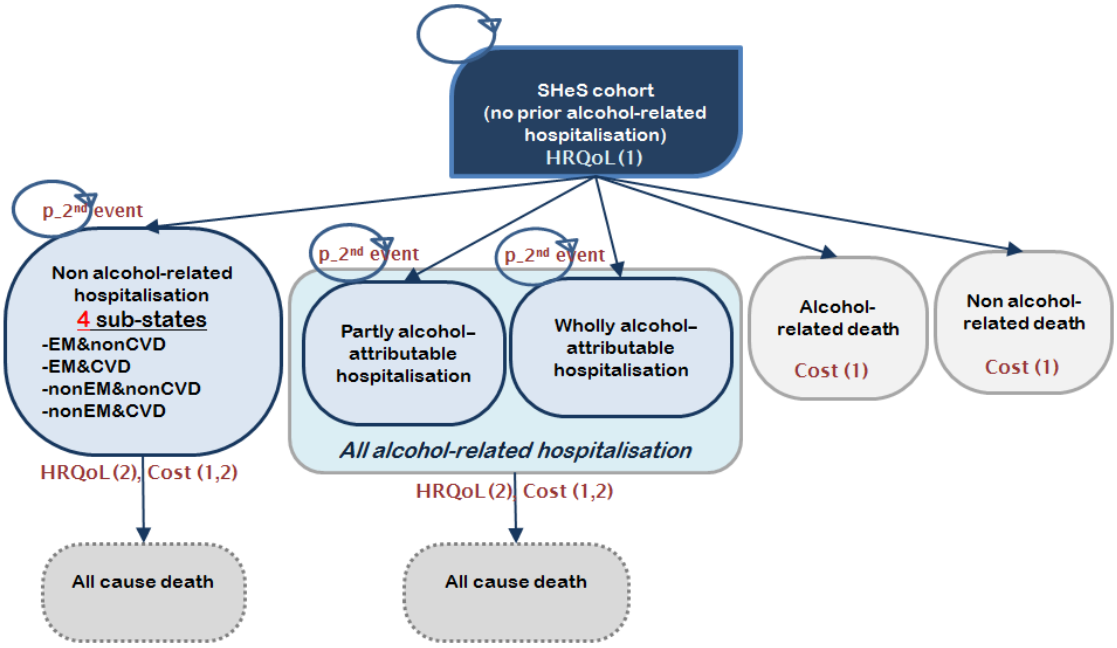
9/ICD-10) of inpatient/day case activity, procedures and diagnoses, day surgery and outpatient procedures, multiple and all emergency admissions, unintentional injuries admitted to National Health Service (NHS) hospitals in Scotland between 1981-2013 (Information Services Division, Fleming et al., 2012). However, total long-term healthcare costs of study population will not be estimated due to a lack of comprehensive information as linkage record with diagnosis e.g. accident and emergency (A&E), outpatient and primary care attendances. Thus, this analysis estimated in particular of remaining QALYs and hospitalisation costs after survey date in long-term. These estimated QALYs and costs will be useful for comparison across risk profiles of the study population.

7.2.1 Overview of the health state transition model

Figure 7-1 illustrates the structure of the alcohol intervention model used for estimating QALY and lifetime hospitalisation costs. Chapter 6 detailed the health state transition model for predicting the competing first events after the survey date as well as death following hospitalisation classified by different risk profiles. Now, this chapter will focus on predicting the QALY and hospitalisation costs in the lifetime horizon after survey date using this model. To estimate QALY, there are three components that need to be identified and valued using statistical function (Figure 7-1) as follows: 1) baseline HRQoL index at the survey date, which is applied as the starting health state of the SHeS cohort as presented by equation HRQoL [1]; 2) reduction in HRQoL (utility decrement) due to alcohol-related (i.e. wholly and partly alcohol attributable conditions) and non-alcohol related (i.e. four sub-states) hospitalisations, which is the impact of the hospitalisation health state on HRQoL as presented by equation HRQoL [2]; and 3) the annual probability of incurring subsequent hospitalisations (i.e. alcohol-related and non-alcohol related conditions) after survival from the first hospitalisation (equation p_2nd event), which is used for adjusting utility decrement classified by alcohol-related and non-alcohol related conditions for the cohort's lifetime horizon.

For estimating lifetime hospitalisation costs, two costs components were estimated as shown in Figure 7-1. Firstly, annual healthcare costs of first events

after the survey date for SHeS cohorts who had first admission (costs of the hospitalisation state) or died within 28 days after admission (costs of the death state) were estimated using a statistical function shown as equation Cost (1); this was designated as either alcohol-related or non-alcohol related. Secondly, annual healthcare costs of subsequent hospitalisations in the following years for those who had yet to experience any first hospitalisations were also calculated using equation Cost (2).



Equation HRQoL (1): Baseline HRQoL= Function (*age at survey date, SIMD, and AUDIT score*) subgroup by gender
Equation HRQoL (2): Reduction of HRQoL due to hospitalisation: Function (*age at survey date, SIMD, hospitalisation condition and admission within 1 year and over 1 year*) subgroup by gender
Equation p_2nd event: Annual probability of incurring each subsequent hospitalisation: Function (*age at first hospitalisation, SIMD, and time spline*) subgroup by gender and first hospitalisation
Equation Cost (1): Annual health care cost of first event: Function (*age at survey date, SIMD, and time spline from survey date*) subgroup by gender
Equation Cost (2): Annual health care cost of subsequent hospitalisation: Function (*age at first hospitalisation, SIMD, and time spline from first hospitalisation*) subgroup by gender and first hospitalisation

SHeS: Scottish Health Survey, EM: Emergency admission, CVD: Cardiovascular disease, HRQoL: Health related quality of life

Figure 7-1 Structure of the health state transition model for estimating QALYs and lifetime hospitalisation costs

7.2.2 Data modelling for predicting QALY

Modelling stage I: Estimating the baseline HRQoL score and utility decrement due to hospitalisation and increasing AUDIT score

The estimation of the HRQoL score and utility decrement associated with alcohol drinking was described in Chapter 5. In summary, the SHeS 2003 participants were measured using the SF-12 (Gray and Leyland, 2005)-a self-reported generic measure of health status as shown in Appendix 4 (Ware et al., 2001). However, the measured SF-12 cannot be used for calculating QALY as that requires a preference-based single index measure of health in terms of the utility index. Brazier and Roberts (2004) developed the estimation of utility score from the SF-6D (SF-12) coefficient as presented in Table 5-1 of Chapter 5 (Brazier and Roberts, 2004). Then, the baseline SF-6D (SF-12) score of the SHeS 2003 participants were presented as the average HRQoL score classified by aged groups, gender and SIMD quintiles.

To estimate the impact of hospitalisation on HRQoL reduction (utility decrement), a multiple linear regression of the current HRQoL was conducted inclusive of prior hospitalisation in compared to no prior hospitalisation (reference group), and further classified into four groups: 1) prior wholly alcohol-related hospitalisation; 2) prior partly alcohol-related hospitalisation; 3) prior CVD hospitalisation; and 4) prior non-CVD hospitalisation. Moreover, the period of each hospitalisation was also categorised to be within the last year and over one year. To define each hospitalisation before the interview date, the SHeS-SMR linkage data was explored using the ICD-9 and ICD-10 list as shown in Appendix 1 to classify those hospitalisations. Additionally, the relationship between alcohol use measured by the AUDIT and HRQoL was examined via the multivariate analysis. Other covariates, which were found to have an independent relationship with HRQoL were also taken into account, i.e. age at survey date and SIMD (Gray and Leyland, 2005, Office of the Chief Statistician, 2004).

Modelling stage II: Estimating risk of having subsequent hospitalisations after the first hospitalisation

Following the first hospitalisation after the survey date, the model predicted survival and life expectancy of the SHeS cohort as detailed in Chapter 6. Furthermore, individuals who survived after the first hospitalisation are at risk of subsequent hospitalisations in the following years, and these re-admissions affect to the amount of the HRQoL is reduced; therefore, estimating QALYs also takes into account the utility decrement due to subsequent hospitalisations. Thus, the risks of having subsequent hospitalisations were estimated using the SHeS-SMR linkage records of individuals who experienced the first hospitalisation, and those hospitalised patient records were analysed separately as patients who had either an alcohol-related or non-alcohol related hospitalisation as the first hospitalisation. Furthermore, males and females were modelled separately. The ICD-9 and ICD-10 codes (Appendix 1) presented as the principal diagnosis (the primary reason for admission) was used to identify the subsequent hospitalisations classified into be 6 conditions: 1) wholly alcohol-attributable hospitalisation; 2) partly alcohol-attributable hospitalisation; 3) non-emergency (EM) admission and non-cardiovascular disease (CVD); 4) non-EM admission with CVD; 5) EM admission and non-CVD; and 6) EM admission with CVD.

The aim of the analysis was to predict the annual probability that an individual who experienced alcohol-related and non-alcohol related hospitalisation would have any of that six-subsequent events conditional upon being alive at a certain point in time. The modelling average observed event count assumed that all individuals in the same subgroup (classified by gender and first hospitalisation) had the same risk profile. The maximum follow-up in the SHeS-SMR linkage record was approximately 19 years. To apply the model, developing a multivariate analysis using observed data would allow for the extrapolation of a 100-year period as the model cycle length. For the purpose of prediction, piecewise polynomials of an order higher than linear was used because even though the linear spline is simple and can approximate many common relationships, it is not smooth and will not fit highly curved functions

well (Harrell, 2015); this method can overcome these problems. Cubic polynomials have been found to have nice properties with a good ability to fit sharply-curving shapes (Harrell et al., 1988, Smith, 1979). Cubic splines can be smoothened at the joint points (knots) by forcing the first and second derivatives of the function to agree at the knots. Since cubic spline regression models are piecewise polynomials, splines can be fitted to any existing regression programme once certain derived predictors are constructed. Thus, flexible forms of the relationship between the predictor and response can be specified with equal ease in all multiple regression models (Harrell et al., 1988).

This analysis employed the restricted cubic splines to extrapolate observation, because the truncated power for restricted cubic splines allows for rational extrapolation beyond the outer knots (Harrell, 2015). For the first stage, the observed period was divided into equally-spaced percentiles, and the frequency of first event rates was estimated within each percentile. In the second stage, a set of knots was chosen which grouped the data into segments. Following Harrell's guideline for STATA (Harrell, 2015), three knots were chosen to generate three segments; this allowed for piecewise regression between adjacent knots. When using restricted cubic splines, one obtains a continuous smooth function that is linear before the first knot, a piecewise cubic polynomial between adjacent knots, and linear again after the last knot. The restricted cubic splines function in STATA selects knots automatically based on the events frequencies across percentiles.

The average event count per annual cycle of the model was estimated, by dividing the number of individuals having an event by the total number of alive SHeS cohorts. A multiple regression model was employed to estimate the annual risks of experiencing each subsequent hospitalisation utilising the covariates age at first hospitalisation and SIMD, and further sub-grouped by gender and first hospitalisations as mentioned above. In addition, the restricted cubic splines of time from the first hospitalisation were included in the modelling to predict the risk of event related to the period. It was noted that the time splines were different between the first hospitalisation even though these were similar across subsequent events and gender. A probit model was

selected based on the assumptions that the event proportions were continuous, ranging from 0 to 1, and following a standard normal distribution.

Modelling stage III: Estimating QALY

Following the estimations of baseline utility, utility decrement due to hospitalisation, and risk of having subsequent hospitalisation over the lifetime period, this stage describes how these estimations are input into the alcohol intervention model to estimate QALYs using HRQoL adjusted for survival as estimated and detailed in Chapter 6: (Billingham and Abrams, 2002, Billingham et al., 1999). This approach combined the amount of time patients spent in a number of different health states with weights reflecting the HRQoL of those health states to create a composite measure of quality (referred to as utility) and quantity of life (Billingham and Abrams, 2002). Figure 7-1 is the health state transition model of this analysis. Based on the population level approach, the HRQoL of different health states which were derived from modelling stage I were combined with the survival function in each health state as represented by (Billingham and Abrams, 2002, Gray et al., 2011b):

$$QALY\ (T) = \int_0^T Q(t)S(t)$$

where $S(t)$ is the proportion of cohorts that survive to time t and $Q(t)$ is the average HRQoL score of those survivors, which is then integrated between zero and fixed time T. Hence, the quality-adjusted survival curve is formed by plotting against time t, the product of the mean HRQoL score of patients alive at time t, and the probability of surviving to time t.

There are four stages of the alcohol intervention model for predicting QALYs. Firstly, the starting SHeS cohort without any prior alcohol-related event was assigned a baseline utility by age at the survey date, gender, SIMD, and drinking behaviour as measured by the AUDIT (derived from modelling stage I). Secondly, the survival cohort who remained not hospitalised was adjusted by only the baseline HRQoL until death. For cohorts who experienced first

hospitalisation after the survey date, the reduction of HRQoL (utility decrement) was accounted for in the year of life when the first hospitalisation occurred and further classified by hospitalisation conditions (derived from modelling stage I). Thirdly, hospitalised patients had the risk of incurring subsequent admissions (derived from modelling stage II) so the effect of these hospitalisations on HRQoL and the annual risk of having following admissions were used for adjusting life year. Finally, the sum of quality-adjusted survival of each annual cycle in different health states was calculated for over 100 cycles and presented by the remaining QALYs for cohorts who remained alive.

7.2.3 Data modelling for predicting lifetime hospitalisation costs

Modelling stage I: Identifying the data source for estimating hospitalisation costs

Similar to previous analyses, this analysis used the SHeS-SMR linkage data (SMR01, acute inpatient and day cases) as described in Chapter 3. For each episode of hospitalisation after survey date, ICD-9 and ICD-10 codes were used to record the primary diagnosis up to the sixth diagnosis as well as to define whether the hospitalisation was alcohol-related or non-alcohol related as shown in Appendix 1. The length of stay (LOS) was also recorded. SHeS-SMR01 participants were followed up from the survey date either until death or the end of the study period on 31st December 2013. For estimating healthcare costs, the resource of cost information was obtained from the Scottish health services costs ('Cost book') in 2013 (Information Services Division (ISD), 2013). The costs are specified by each of the 14 regional health boards and specialty code related to admission condition as provide the listing cost by ISD Scotland (Information Services Division (ISD), 2015).

Modelling stage II: Estimating annual hospitalisation costs in the year of having first event and the following years

Geue et al. in 2012 compared alternative costing methods of hospitalisation episode, and the study recommended the application of the healthcare resource groups (HRG) costing method (Geue et al., 2012). This method is a measure of case mix by presenting standard groupings for clinically similar treatments, which use a common set of healthcare resources (The Health and Social Care Information Centre, 2016). However, the limitation of this method for Scottish data was that costs for inpatient hospitalisation episodes were not available on an HRG level, only at specialty level. The purpose of the current study is to model the predicted lifetime healthcare cost among specific risk profiles for economic evaluation which all future costs are discounted based on HTA guidelines (ISPOR, 2014, NICE, 2013, Chaikledkaew and Kittrongsiri, 2014, Teerawattananon and Chaikledkaew, 2008); as such, the actual hospital episode cost might not be estimated. Thus, per diem costing (method 3 from Geue et al., 2012) -which has been used for economic evaluation- is applied to this study using the Scottish health services costs as specified by 14 health boards and specialty (Information Services Division (ISD), 2015, Information Services Division (ISD), 2013). The total costs per episode were calculated by the cost per bed day of the specific specialty and health board multiplied by individual LOS (Geue et al., 2012). To define the trim-point of cost per episode, any LOS longer than 28 days was excluded from this analysis (3,395 of 172,704 episodes) because long stay costs were not included in the Cost Book, and the mean of LOS was only 4.38 (95% CI 4.23, 4.53).

Total annual costs per case were estimated by the sum of all hospital episodes in each year. The annual costs were modelled separately to be the annual healthcare cost in the year of occurring first event (equation Cost1 in Figure 7-1) and the following years after first event (equation Cost2 in Figure 7-1). To model annual costs of following hospitalisations after the first event, the hospitalised patients were divided by first hospitalisation condition, i.e. alcohol-related or non-alcohol related hospitalisation; and the annual healthcare cost of subsequent hospitalisations in following years were also

modelled separately. Based on previous literature, the alternative approaches of modelling healthcare costs have been frequently discussed (Basu and Manning, 2009, Jones et al., 2015a, Briggs et al., 2005, Nixon and Thompson, 2004, Dodd et al., 2006). The most recommended approach is fitting a generalised linear model (GLM) using a gamma distribution with log-link function as described in Chapter 4 (McCullagh and Nelder, 1989). This was found to be a good performance predictor for cost distribution (Dodd et al., 2006, Jones et al., 2015a).

The GLM using gamma distribution with log-link function was employed to estimate the annual cost of each first hospitalisation (equation Cost1) and the annual costs of the following years after the first hospitalisation (equation Cost2), sub-grouped by gender. Modelling healthcare costs also used restricted cubic splines with three knots, similar to modelling the risk of subsequent hospitalisations as mentioned above (Harrell et al., 1988, Smith, 1979). The modelling covariates included age at survey date for equation Cost1, age at first hospitalisation for equation Cost2, and SIMD. In addition, the restricted cubic splines of time from the survey date (equation Cost1) and time spline from the first hospitalisation (equation Cost2) were included in the modelling to predict annual hospitalisation costs related to the time period; the time spline was similar between males and females. These explanatory variables were used to model the log of arithmetic mean cost using the GLM with gamma distribution and log link function, which was performed as:

$$\ln[E(y|x)] = x\beta$$

Modelling stage III: Estimating lifetime hospitalisation costs

To estimate the lifetime hospitalisation costs, the average yearly hospitalisation costs (derived from modelling stage II) were adjusted by predicted survival over the lifetime using the same alcohol intervention model used for estimating QALY (Billingham and Abrams, 2002, Billingham et al., 1999); the predicted survival was described in Chapter 6. This modelling stage combined the predicted annual cost of each year with predicted survival. There were two components of predicting healthcare costs using the alcohol

intervention model. Firstly, SHeS cohorts who were not hospitalised had no predicted cost. For cohorts who experienced first hospitalisation after survey date, the annual hospitalisation cost was estimated in the year of incurring first event classified by hospitalisation conditions (derived from equation Cost1). Secondly, after first hospitalisation, these survival patients had the risk of incurring subsequent admissions in following years, so these subsequent hospitalisations costs (derived from equation Cost2) were adjusted by survival over lifetime. The sum of those two costs for each annual cycle was calculated over 100 cycles and presented as the healthcare costs of the remaining living cohorts.

7.3 Results: Modelling for predicting QALY

7.3.1 Baseline HRQoL score and utility decrement due to hospitalisation and increasing AUDIT score

The baseline SF-6D (SF-12) HRQoL scores of SHeS participants across deprivation quintiles were estimated and classified by gender and aged groups showing the mean and 95% CI in Table 7-1 for males and Table 7-2 for females. It can be seen these baseline HRQoL scores that scores decreased with increasing age and more deprivation status for both males and females. For males, the overall HRQoL score decreased from 0.831 (95% CI 0.808, 0.854) in the least deprived SIMD to 0.754 (95% CI 0.719, 0.79) in the most deprived SIMD. For females, the HRQoL scores between the least and most deprivation were 0.826 (95% CI 0.806, 0.846) and 0.737 (95% CI 0.707, 0.769), respectively. For both genders, the effect of deprivation status on HRQoL was lower in younger aged groups.

As shown in Chapter 5, a multivariate analysis was conducted to investigate the impact of prior hospitalisation on current HRQoL score as presented in Table 7-3, classified by gender. For males, the decrement on HRQoL scores due to prior hospitalisation-where the impacts of having an event within the last year were greater than having an event over 1 year ago ranged from -0.072 (95% CI [-0.113, -0.031], p=0.001) to -0.123 (95% CI [-0.212, -0.033],

p=0.008) for wholly alcohol-related conditions, -0.027 (95% CI [-0.043, -0.012], p=0.001) to -0.069 (95% CI[-0.121, -0.018], p=0.008) for partly alcohol-related condition, as well as -0.043 (95% CI [-0.059, -0.026], p<0.001) for non-alcohol related and non-CVD condition, and a range of -0.078 (95% CI [-0.097, -0.060], p<0.001) to -0.134 (95% CI [-0.178, -0.091], p<0.001) for non-alcohol related with CVD condition. Each unit increase in the predict AUDIT scores was associated with a decrement score of -0.004 (95% CI [-0.006, -0.002], p<0.001).

For females, the decrement on HRQoL scores due to different year of hospitalisations were -0.08 (95% CI [-0.121, -0.039], p<0.001) for wholly alcohol-related condition, a range of -0.043 (95% CI [-0.056, -0.031], p<0.001) to -0.126 (95% CI [-0.172, -0.080], p<0.001) for partly alcohol-related condition, a range of -0.017 (95% CI [-0.027, -0.008], p<0.001) to -0.048 (95% CI [-0.062, -0.033], p<0.001) for non-alcohol related and non-CVD condition, and a range of -0.097 (95% CI [-0.115, -0.078], p<0.001) to -0.109 (95% CI [-0.16, -0.059], p<0.001) for non-alcohol related with CVD condition. Each unit increase of the predicted AUDIT score was associated with a decrement score of -0.002 (95% CI [-0.005, -0.0002], p=0.030), which shows that it had less of an effect on women than men. These utility decrements will be used for further modelling to estimate QALY.

Table 7-1 Baseline SF-6D (SF-12) HRQoL scores of SHeS 2003 participants across fifths of deprivation: males

Aged group (years)	Scottish Index of Multiple Deprivation (SIMD)				
	5th (least deprived)	4th	3rd	2nd	1st (most deprived)
All (N)	(634)	(701)	(691)	(597)	(482)
Mean	0.831	0.826	0.81	0.795	0.754
95% CI	*(0.808, 0.854)*	*(0.803, 0.849)*	*(0.785, 0.836)*	*(0.766, 0.825)*	*(0.719, 0.79)*
18-24 (N)	(23)	(27)	(27)	(32)	(31)
Mean	0.822	0.853	0.834	0.857	0.787
95% CI	*(0.787, 0.857)*	*(0.824, 0.881)*	*(0.795, 0.873)*	*(0.828, 0.887)*	*(0.745, 0.83)*
25-34 (N)	(75)	(88)	(88)	(104)	(70)
Mean	0.848	0.849	0.823	0.816	0.774
95% CI	*(0.826, 0.871)*	*(0.83, 0.867)*	*(0.796, 0.85)*	*(0.794, 0.839)*	*(0.741, 0.807)*
35-44	(146)	(164)	(155)	(125)	(97)
Mean	0.834	0.838	0.823	0.811	0.777
95% CI	*(0.816, 0.852)*	*(0.82, 0.855)*	*(0.805, 0.841)*	*(0.787, 0.835)*	*(0.744, 0.81)*
45-54	(128)	(139)	(126)	(82)	(96)
Mean	0.825	0.827	0.808	0.791	0.762
95% CI	*(0.805, 0.845)*	*(0.806, 0.849)*	*(0.783, 0.833)*	*(0.756, 0.826)*	*(0.729, 0.794)*
55-64	(138)	(127)	(121)	(111)	(80)
Mean	0.845	0.803	0.82	0.782	0.718
95% CI	*(0.826, 0.865)*	*(0.78, 0.826)*	*(0.796, 0.843)*	*(0.751, 0.813)*	*(0.68, 0.757)*
65-74	(86)	(89)	(107)	(92)	(72)
Mean	0.813	0.822	0.802	0.761	0.732
95% CI	*(0.784, 0.841)*	*(0.791, 0.853)*	*(0.775, 0.83)*	*(0.729, 0.792)*	*(0.697, 0.768)*
> 74	(38)	(67)	(67)	(51)	(36)
Mean	0.797	0.802	0.756	0.775	0.732
95% CI	*(0.75, 0.843)*	*(0.77, 0.835)*	*(0.722, 0.791)*	*(0.731, 0.818)*	*(0.685, 0.779)*

Table 7-2 Baseline SF-6D (SF-12) HRQoL scores of SHeS 2003 participants across fifths of deprivation: females

Aged group (years)	Scottish Index of Multiple Deprivation (SIMD)				
	5th (least deprived)	4th	3rd	2nd	1st (most deprived)
All (N)	(784)	(873)	(858)	(749)	(685)
Mean	0.826	0.807	0.785	0.769	0.737
95% CI	(0.806, 0.846)	(0.786, 0.828)	(0.761, 0.809)	(0.743, 0.795)	(0.707, 0.766)
18-24 (N)	(30)	(37)	(36)	(48)	(59)
Mean	0.846	0.81	0.78	0.799	0.816
95% CI	(0.813, 0.88)	(0.779, 0.842)	(0.739, 0.821)	(0.765, 0.832)	(0.787, 0.845)
25-34 (N)	(105)	(122)	(114)	(128)	(104)
Mean	0.839	0.816	0.822	0.803	0.775
95% CI	(0.822, 0.856)	(0.795, 0.836)	(0.803, 0.841)	(0.78, 0.825)	(0.749, 0.8)
35-44 (N)	(176)	(198)	(172)	(150)	(142)
Mean	0.837	0.827	0.794	0.788	0.748
95% CI	(0.823, 0.852)	(0.812, 0.841)	(0.773, 0.815)	(0.769, 0.808)	(0.722, 0.774)
45-54 (N)	(180)	(166)	(157)	(128)	(117)
Mean	0.827	0.793	0.78	0.769	0.736
95% CI	(0.812, 0.843)	(0.773, 0.812)	(0.758, 0.802)	(0.745, 0.792)	(0.708, 0.764)
55-64 (N)	(133)	(162)	(167)	(126)	(105)
Mean	0.835	0.815	0.791	0.769	0.701
95% CI	(0.816, 0.854)	(0.798, 0.832)	(0.768, 0.814)	(0.742, 0.796)	(0.67, 0.732)
65-74 (N)	(96)	(102)	(118)	(86)	(87)
Mean	0.827	0.803	0.792	0.742	0.702
95% CI	(0.803, 0.851)	(0.776, 0.83)	(0.766, 0.818)	(0.709, 0.776)	(0.668, 0.736)
> 74 (N)	(64)	(86)	(94)	(83)	(71)
Mean	0.741	0.765	0.715	0.693	0.689
95% CI	(0.702, 0.779)	(0.732, 0.798)	(0.681, 0.748)	(0.655, 0.731)	(0.652, 0.726)

Table 7-3 Utility decrement due to hospitalisation and increasing AUDIT score

Condition	Utility decrement*									
	Males (n=3,105)					Females (n=3,949)				
	Mean	SE	*p-value*	95%CI		Mean	SE	*p-value*	95%CI	
Increasing each AUDIT score by 1**	-0.004	0.001	*<0.001*	-0.006	-0.002	-0.002	0.001	*0.030*	-0.005	-0.0002
Wholly alcohol-related hospitalisation										
within 1 year	-0.123	0.046	*0.008*	-0.212	-0.033	0.031	0.099	*0.755*	-0.163	0.225
over 1 year	-0.072	0.021	*0.001*	-0.113	-0.031	-0.080	0.021	*<0.001*	-0.121	-0.039
Partly alcohol-related hospitalisation										
within 1 year	-0.069	0.026	*0.008*	-0.121	-0.018	-0.126	0.024	*<0.001*	-0.172	-0.080
over 1 year	-0.027	0.008	*0.001*	-0.043	-0.012	-0.043	0.006	*<0.001*	-0.056	-0.031
Non-CVD hospitalisation										
within 1 year	-0.043	0.008	*<0.001*	-0.059	-0.026	-0.048	0.007	*<0.001*	-0.062	-0.033
over 1 year	-0.009	0.005	*0.085*	-0.020	0.001	-0.017	0.005	*<0.001*	-0.027	-0.008
CVD hospitalisation										
within 1 year	-0.134	0.022	*<0.001*	-0.178	-0.091	-0.109	0.026	*<0.001*	-0.160	-0.059
over 1 year	-0.078	0.009	*<0.001*	-0.097	-0.060	-0.097	0.010	*<0.001*	-0.115	-0.078

*Utility decrement value after adjusting for age at survey date and SIMD deprivation index

**The effect of increasing each unit of the AUDIT score from 0 to 40

7.3.2 Risk of having subsequent hospitalisation after the first hospitalisation

Figure 7-2 to Figure 7-13 illustrate the graphs of observed proportions of subsequent hospitalisations after the first hospitalisation (i.e. alcohol-related and non-alcohol related hospitalisations), classified by gender and six subsequent hospitalisations for a 19-year follow-up period. In general, the observed proportions of subsequently hospitalised patients following the first alcohol-related hospitalisation were unstable over the follow-up period. In contrast, the observed proportions of those patients who experienced the first non-alcohol related admission were uniform over time. The highest proportion of observed subsequent hospitalisations was non-emergency admission with non-CVD condition for both men and women, followed by emergency admission and non-CVD condition.

The modelling predicted the risks of having six subsequent hospitalisations after first events by using separate models defined by gender and first hospitalisation condition (i.e. alcohol-related and non-alcohol related conditions). The coefficients of the probit model are shown in Table 7-4 and Table 7-5, and the restricted cubic spline of time since the first event are represented in Table 7-6 for subsequent events after first alcohol-related hospitalisation. The probit model results of subsequent events post-non-alcohol related admission are shown Table 7-7 and Table 7-8, and the time spline covariate is shown in Table 7-9. As shown by the estimated coefficients, the risks of incurring six subsequent events were different compared between two hospitalised patients who had experienced alcohol-related and non-alcohol related hospitalisations. In addition, there were differences in the coefficients compared between men and women as well, which could support the justification of using separated model by first hospitalisation type and gender. Moreover, there were subsequent modelled events where the coefficients of time spline, age at first events, and SIMD were reported to be statistically significant. Overall, the results suggest that the further six hospitalisations are related to these modelling covariates and different risks between gender as well as between first hospitalisation type.

Figure 7-2 Observed proportions of wholly alcohol-related hospitalisation after the year of occurring first event: males

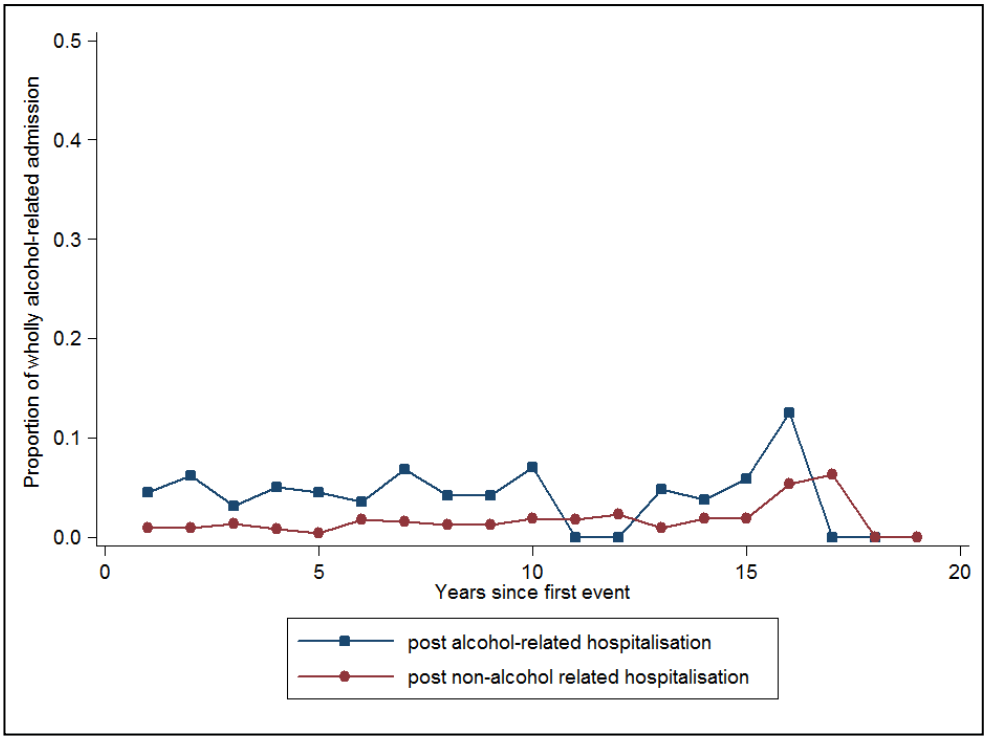


Figure 7-3 Observed proportions of wholly alcohol-related hospitalisation after the year of occurring first event: females

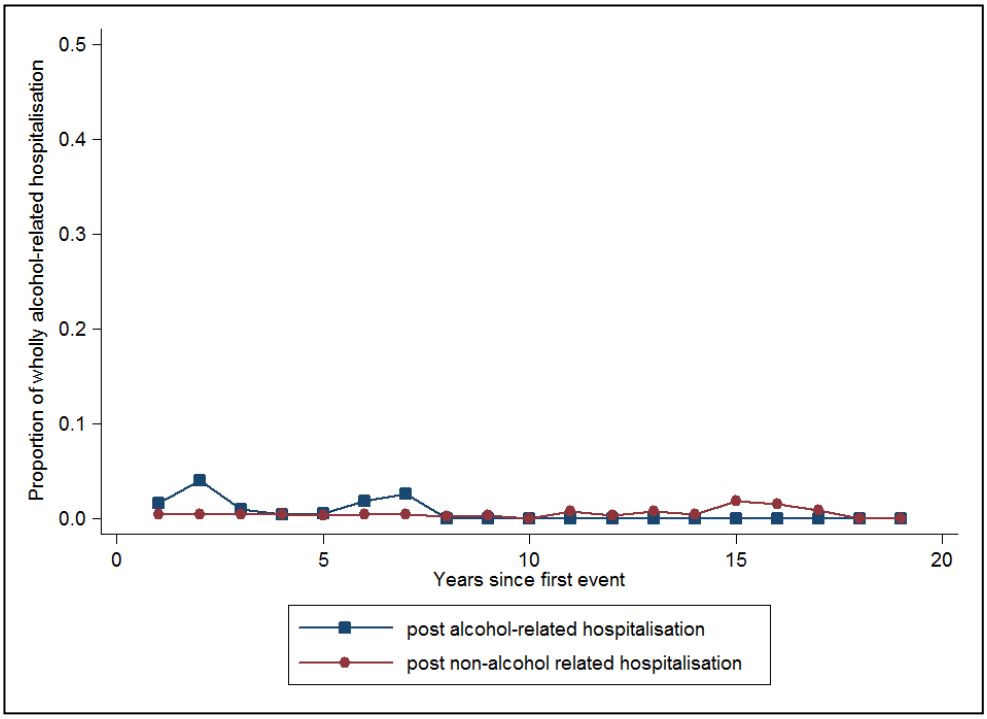


Figure 7-4 Observed proportions of partly alcohol-related hospitalisation after the year of occurring first event: males

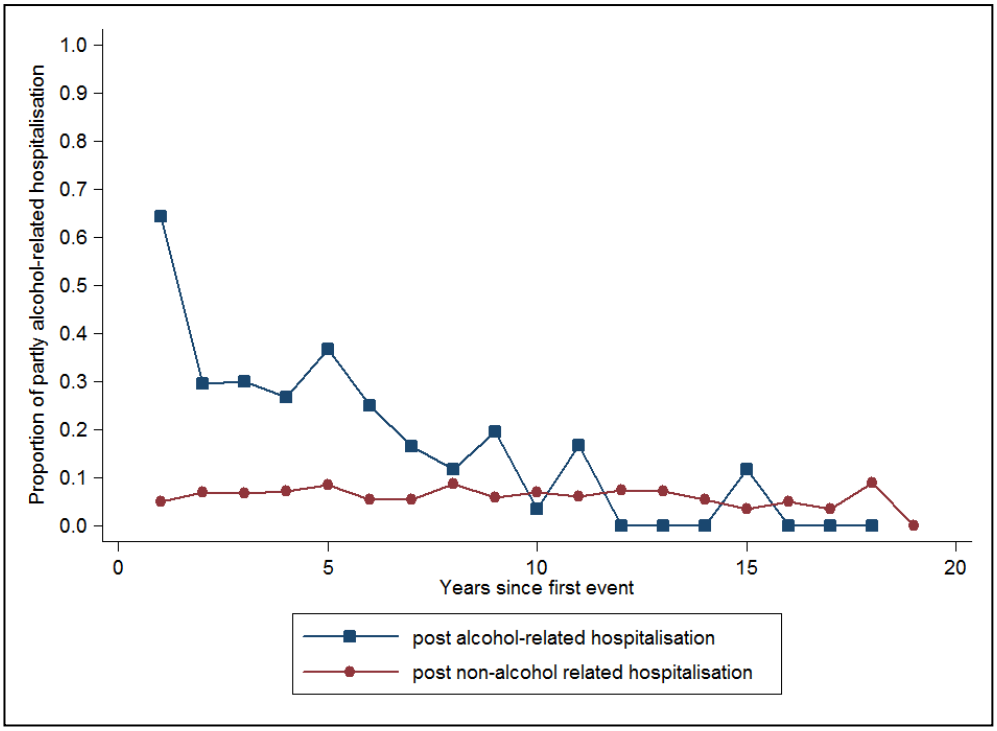


Figure 7-5 Observed proportions of partly alcohol-related hospitalisation after the year of occurring first event: females

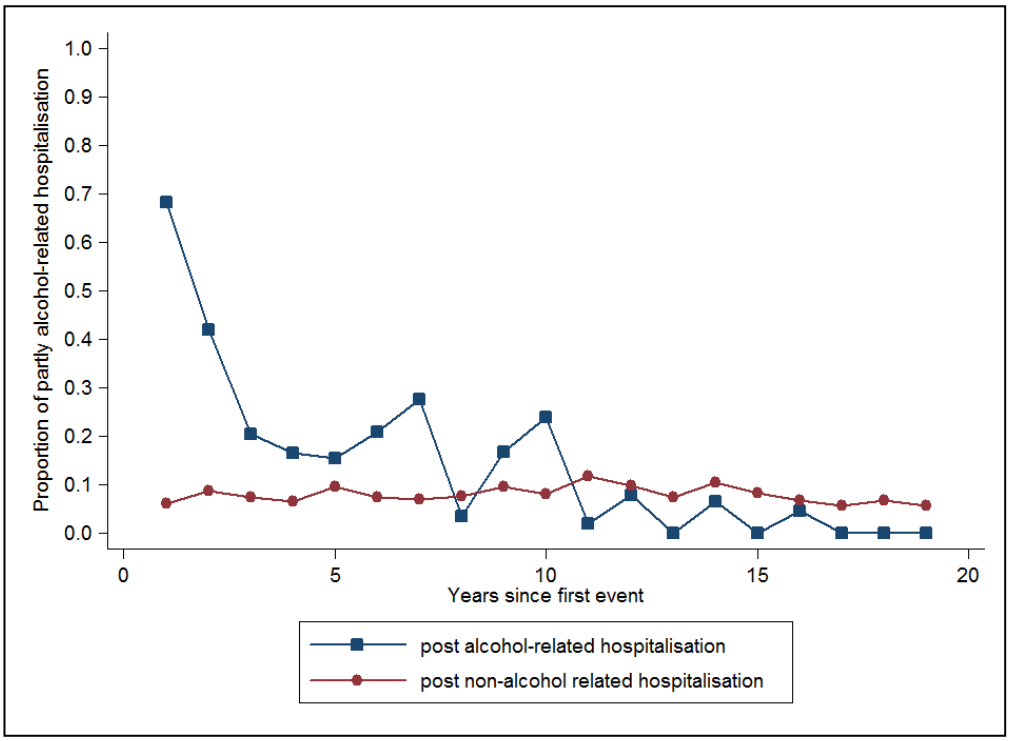


Figure 7-6 Observed proportions of non-emergency and non-CVD admission after the year of occurring first event: males

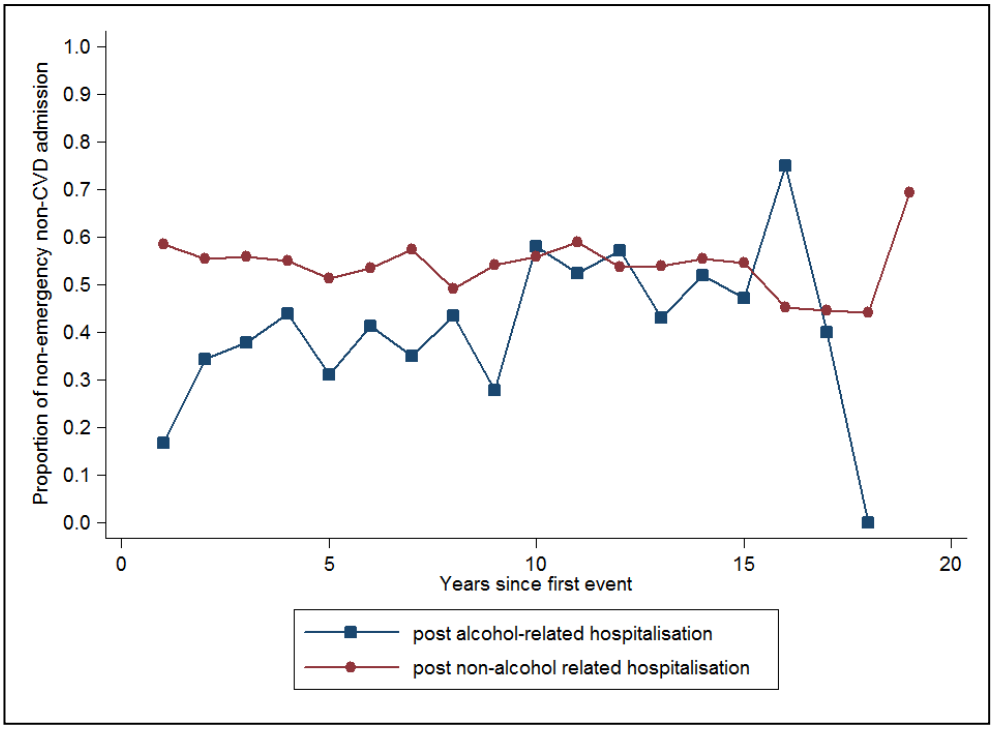


Figure 7-7 Observed proportions of non-emergency and non-CVD admission after the year of occurring first event: females

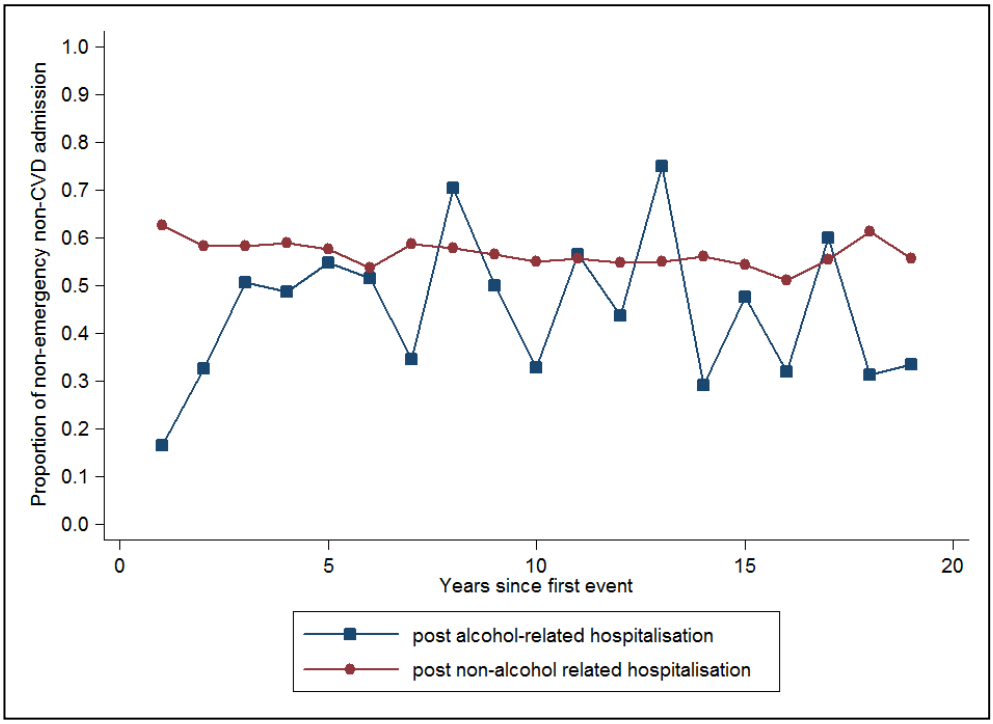


Figure 7-8 Observed proportions of non-emergency and CVD admission after the year of occurring first event: males

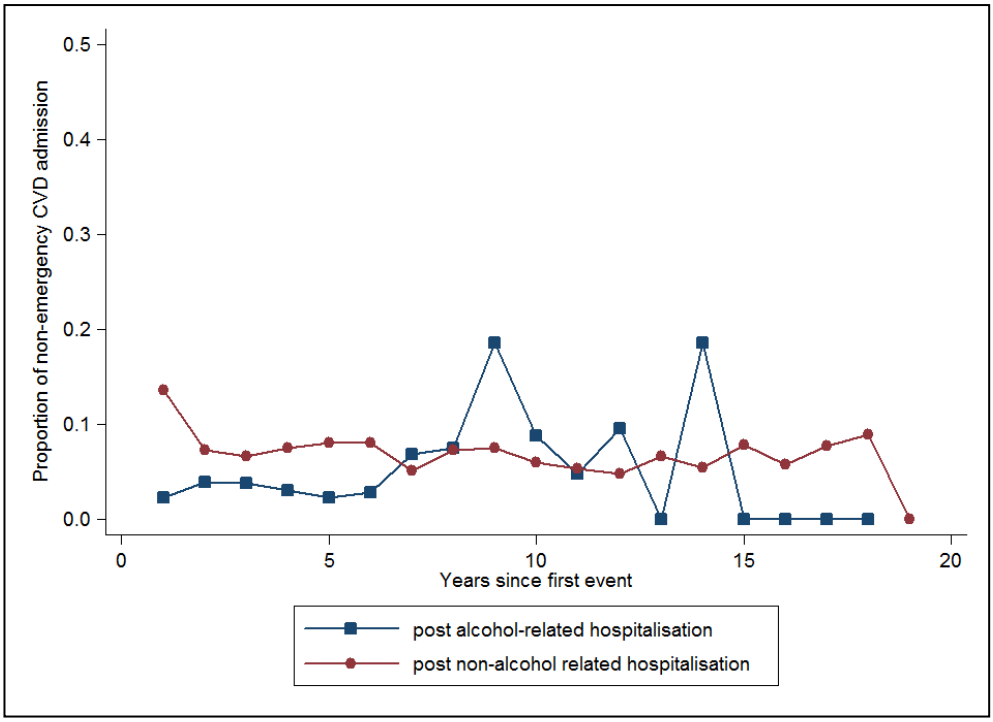


Figure 7-9 Observed proportions of non-emergency and CVD admission after the year of occurring first event: females

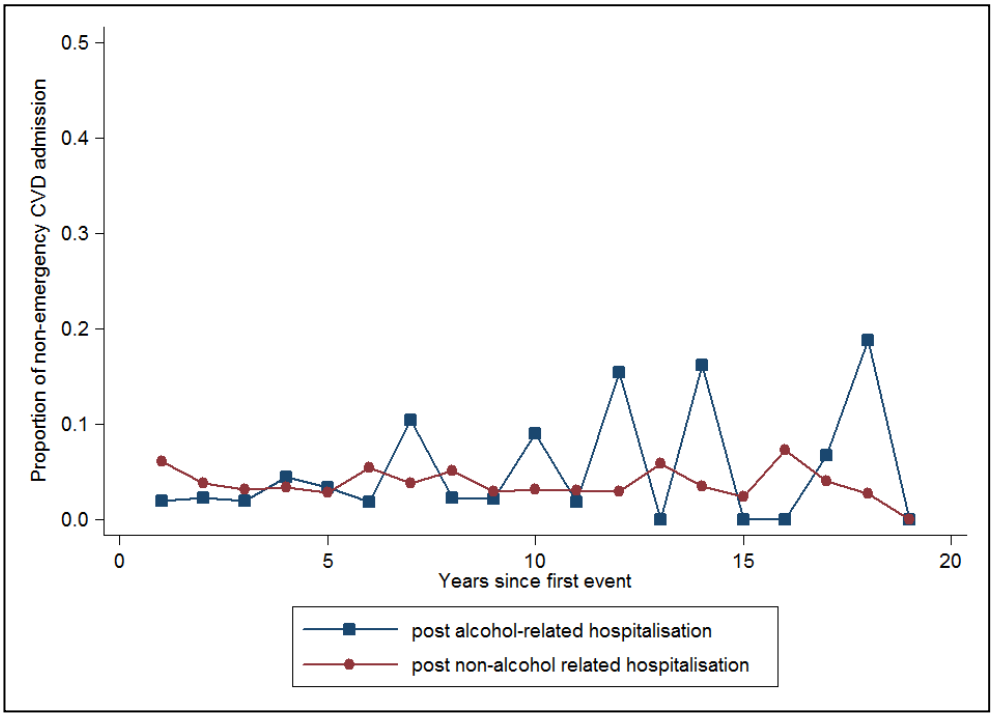


Figure 7-10 Observed proportions of emergency and non-CVD admission after the year of occurring first event: males

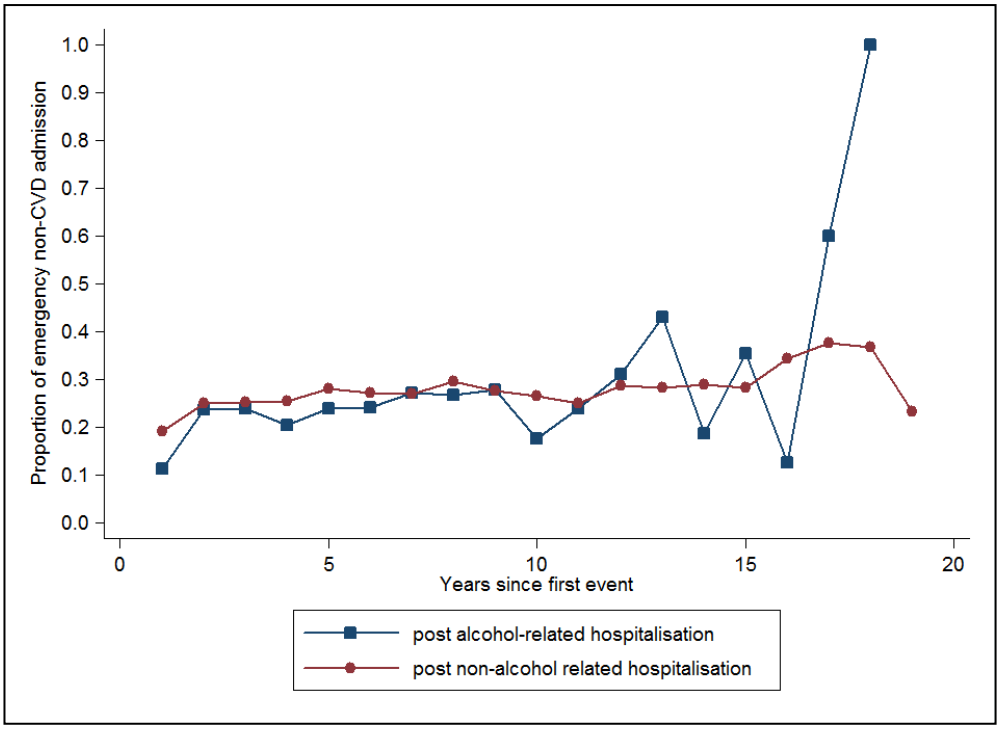


Figure 7-11 Observed proportions of emergency and non-CVD admission after the year of occurring first event: females

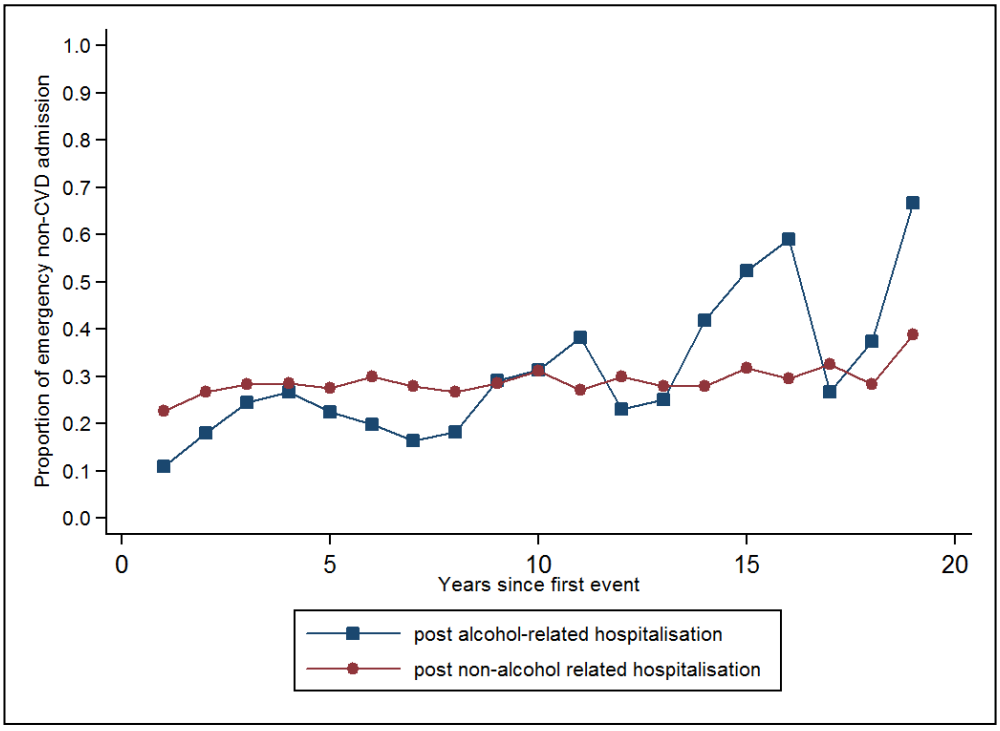


Figure 7-12 Observed proportions of emergency and CVD admission after the year of occurring first event: males

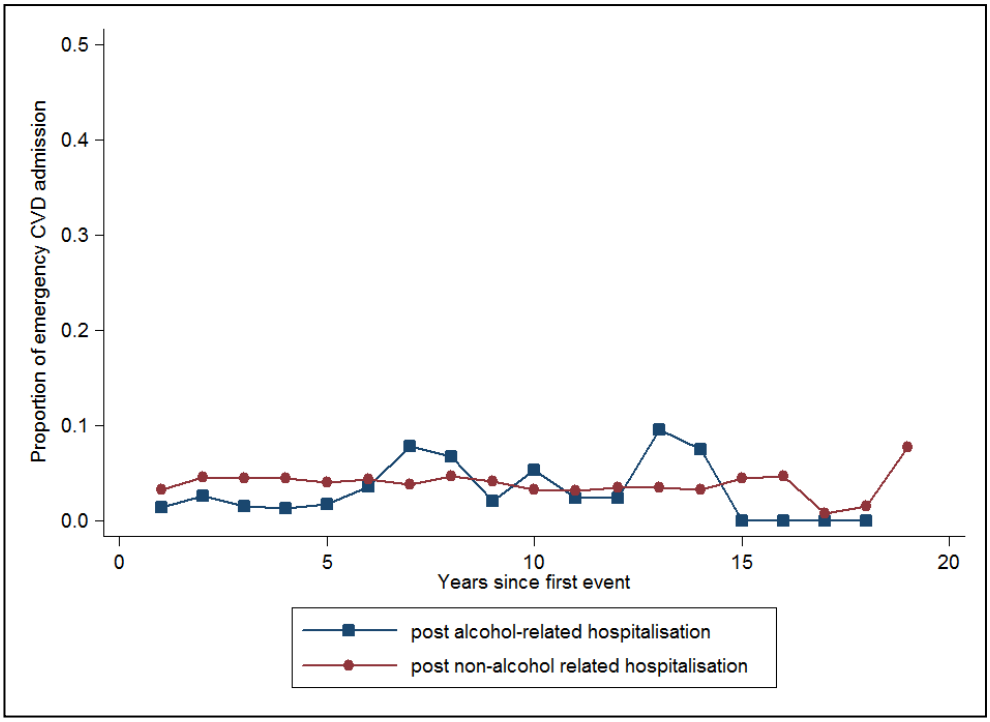


Figure 7-13 Observed proportions of emergency and CVD admission after the year of occurring first event: females

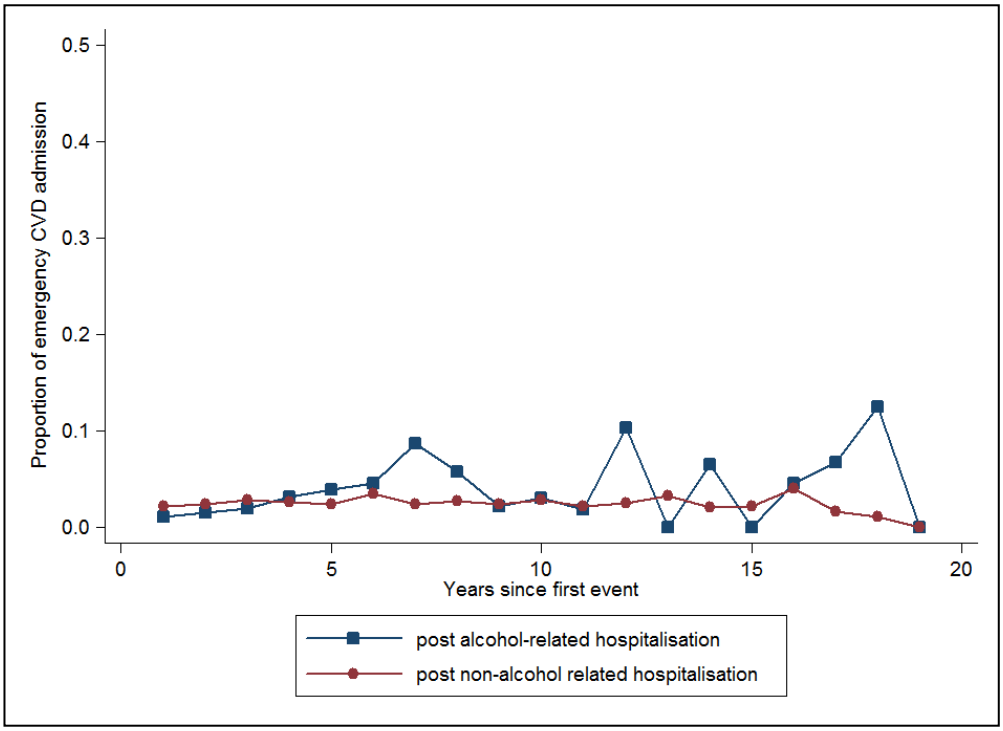


Table 7-4 Modelling the risk of 6 subsequent events *following alcohol-related hospitalisation (n=445)*: males

	a) wholly alcohol-related hospitalisation				b) partly alcohol-related hospitalisation				c) emergency admission and non-CVD condition			
Covariate	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***
timespline1	-0.079	-0.239	0.081	*0.332*	-0.365	-0.518	-0.212	*<0.001*	0.182	0.100	0.263	*<0.001*
timespline2	0.074	-0.599	0.746	*0.830*	0.826	0.264	1.388	*0.004*	-0.510	-0.814	-0.206	*0.001*
Age at first event	-0.028	-0.045	-0.011	*0.001*	0.003	-0.006	0.013	*0.503*	-0.003	-0.009	0.002	*0.228*
SIMD (ref.=most deprived)												
2nd	-0.335	-1.057	0.388	*0.364*	-0.186	-0.650	0.278	*0.432*	0.045	-0.200	0.289	*0.721*
3rd	-0.383	-0.966	0.200	*0.198*	-0.142	-0.579	0.295	*0.523*	0.021	-0.224	0.266	*0.866*
4th	-0.540	-1.316	0.235	*0.172*	-0.049	-0.524	0.427	*0.841*	-0.056	-0.320	0.209	*0.680*
5th(least deprived)	-0.700	-1.379	-0.021	*0.043*	-0.079	-0.581	0.422	*0.756*	-0.017	-0.311	0.277	*0.910*
Constant	0.385	-0.683	1.453	*0.480*	0.503	-0.110	1.115	*0.108*	-1.095	-1.481	-0.709	*<0.001*

Table 7-4 Modelling the risk of 6 subsequent events *following alcohol-related hospitalisation (n=445)*: males (cont.)

	d) emergency admission and CVD condition				**e) non-emergency admission and non-CVD condition**				**f) non-emergency admission and CVD condition**			
Covariate	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***
Time spline1	0.114	-0.010	0.238	*0.072*	0.261	0.159	0.363	*<0.001*	0.107	-0.034	0.248	*0.135*
Time spline2	-0.195	-0.617	0.228	*0.367*	-0.692	-1.060	-0.324	*<0.001*	-0.105	-0.561	0.352	*0.654*
Age at first event	0.020	0.010	0.030	*<0.001*	0.002	-0.004	0.009	*0.493*	0.016	0.008	0.024	*<0.001*
SIMD (ref.=most deprived)												
2nd	0.316	-0.051	0.683	*0.092*	0.181	-0.144	0.505	*0.275*	0.120	-0.428	0.668	*0.667*
3rd	0.140	-0.255	0.535	*0.487*	0.169	-0.126	0.464	*0.262*	0.163	-0.356	0.683	*0.538*
4th	0.056	-0.348	0.460	*0.788*	0.268	-0.074	0.610	*0.124*	-0.038	-0.590	0.514	*0.893*
5th(least deprived)	0.106	-0.376	0.589	*0.666*	0.184	-0.167	0.535	*0.304*	0.343	-0.179	0.865	*0.198*
Constant	-3.736	-4.519	-2.953	*<0.001*	-1.428	-1.919	-0.938	*<0.001*	-3.267	-4.042	-2.492	*<0.001*

Table 7-5 Modelling the risk of 6 subsequent events *following alcohol-related hospitalisation (n=614)*: females

	a)wholly alcohol-related hospitalisation				b) partly alcohol-related hospitalisation				c) emergency admission and non-CVD condition			
Covariate	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***
Time spline1	0.060	-0.079	0.200	*0.397*	-0.543	-0.709	-0.378	*<0.001*	0.146	0.066	0.226	*<0.001*
Time spline2	-0.693	-1.498	0.112	*0.091*	1.368	0.796	1.940	*<0.001*	-0.284	-0.562	-0.006	*0.045*
Age at first event	-0.015	-0.029	-0.002	*0.025*	-0.010	-0.018	-0.002	*0.010*	0.007	0.001	0.013	*0.019*
SIMD (ref.=most deprived)												
2nd	0.238	-0.327	0.802	*0.409*	-0.117	-0.501	0.268	*0.551*	-0.268	-0.527	-0.009	*0.042*
3rd	0.653	-0.129	1.436	*0.102*	0.058	-0.326	0.441	*0.768*	-0.402	-0.625	-0.178	*<0.001*
4th	-0.340	-0.973	0.293	*0.292*	0.301	-0.153	0.754	*0.194*	-0.521	-0.791	-0.252	*<0.001*
5th(least deprived)	-0.126	-0.876	0.625	*0.743*	0.147	-0.227	0.522	*0.440*	-0.371	-0.623	-0.119	*0.004*
Constant	-1.473	-2.197	-0.749	*<0.001*	1.520	0.902	2.138	*<0.001*	-1.467	-1.914	-1.020	*<0.001*

Table 7-5 Modelling the risk of 6 subsequent events *following alcohol-related hospitalisation (n=614)*: females (cont.)

	d) emergency admission and CVD condition				**e) non-emergency admission and non-CVD condition**				**f) non-emergency admission and CVD condition**			
Covariate	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***
Time spline1	0.215	0.074	0.356	*0.003*	0.428	0.320	0.535	*<0.001*	0.101	-0.063	0.266	*0.228*
Time spline2	-0.481	-0.954	-0.007	*0.047*	-1.278	-1.643	-0.913	*<0.001*	-0.115	-0.665	0.435	*0.683*
Age at first event	0.022	0.013	0.032	*<0.001*	0.001	-0.006	0.008	*0.752*	0.019	0.006	0.031	*0.004*
SIMD (ref.=most deprived)												
2nd	-0.060	-0.467	0.348	*0.774*	0.290	0.015	0.565	*0.039*	0.191	-0.364	0.747	*0.500*
3rd	0.263	-0.145	0.670	*0.206*	0.091	-0.163	0.345	*0.482*	0.293	-0.218	0.803	*0.261*
4th	-0.069	-0.506	0.368	*0.757*	0.121	-0.204	0.445	*0.467*	-0.014	-0.546	0.517	*0.958*
5th(least deprived)	-0.011	-0.435	0.412	*0.958*	0.165	-0.155	0.485	*0.312*	0.081	-0.423	0.585	*0.753*
Constant	-4.064	-4.816	-3.311	*<0.001*	-1.567	-2.052	-1.082	*<0.001*	-3.518	-4.478	-2.557	*<0.001*

Table 7-6 Time spline variable of modelling the risk of subsequent events *following alcohol-related hospitalisation*

Cycle (year)	Time spline1	Time spline2	Cycle (year)	Time spline1	Time spline2	Cycle (year)	Time spline1	Time spline2
1	1	0	35	35	11.625	68	68	24
2	2	0.0156	36	36	12	69	69	24.375
3	3	0.1071	37	37	12.375	70	70	24.75
4	4	0.279	38	38	12.75	71	71	25.125
5	5	0.5179	39	39	13.125	72	72	25.5
6	6	0.8103	40	40	13.5	73	73	25.875
7	7	1.1429	41	41	13.875	74	74	26.25
8	8	1.5022	42	42	14.25	75	75	26.625
9	9	1.875	43	43	14.625	76	76	27
10	10	2.25	44	44	15	77	77	27.375
11	11	2.625	45	45	15.375	78	78	27.75
12	12	3	46	46	15.75	79	79	28.125
13	13	3.375	47	47	16.125	80	80	28.5
14	14	3.75	48	48	16.5	81	81	28.875
15	15	4.125	49	49	16.875	82	82	29.25
16	16	4.5	50	50	17.25	83	83	29.625
17	17	4.875	51	51	17.625	84	84	30
18	18	5.25	52	52	18	85	85	30.375
19	19	5.625	53	53	18.375	86	86	30.75
20	20	6	54	54	18.75	87	87	31.125
21	21	6.375	55	55	19.125	88	88	31.5
22	22	6.75	56	56	19.5	89	89	31.875
23	23	7.125	57	57	19.875	90	90	32.25
24	24	7.5	58	58	20.25	91	91	32.625
25	25	7.875	59	59	20.625	92	92	33
26	26	8.25	60	60	21	93	93	33.375
27	27	8.625	61	61	21.375	94	94	33.75
28	28	9	62	62	21.75	95	95	34.125
29	29	9.375	63	63	22.125	96	96	34.5
30	30	9.75	64	64	22.5	97	97	34.875
31	31	10.125	65	65	22.875	98	98	35.25
32	32	10.5	66	66	23.25	99	99	35.625
33	33	10.875	67	67	23.625	100	100	36
34	34	11.25						

Table 7-7 Modelling the risk of 6 subsequent events *following non-alcohol related hospitalisation (n=9,053)*: males

	a) wholly alcohol-related hospitalisation				b) partly alcohol-related hospitalisation				c) emergency admission and non-CVD condition			
Covariate	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***
Time spline1	-0.013	-0.072	0.046	*0.672*	0.053	0.015	0.091	*0.007*	0.055	0.036	0.074	*<0.001*
Time spline2	0.047	-0.061	0.154	*0.393*	-0.080	-0.150	-0.010	*0.025*	-0.074	-0.113	-0.035	*<0.001*
Age at first event	-0.017	-0.021	-0.013	*<0.001*	0.010	0.007	0.014	*<0.001*	-0.004	-0.006	-0.002	*0.001*
SIMD (ref.=most deprived)												
2nd	-0.248	-0.526	0.031	*0.081*	0.052	-0.096	0.199	*0.495*	-0.156	-0.248	-0.064	*0.001*
3rd	-0.322	-0.588	-0.056	*0.018*	0.050	-0.110	0.210	*0.543*	-0.129	-0.215	-0.044	*0.003*
4th	-0.366	-0.672	-0.061	*0.019*	-0.010	-0.176	0.157	*0.910*	-0.153	-0.244	-0.061	*0.001*
5th(least deprived)	-0.391	-0.717	-0.065	*0.019*	-0.089	-0.254	0.077	*0.295*	-0.278	-0.400	-0.156	*<0.001*
Constant	-1.134	-1.476	-0.791	*<0.001*	-2.333	-2.598	-2.069	*<0.001*	-0.528	-0.680	-0.375	*<0.001*

Table 7-7 Modelling the risk of 6 subsequent events *following non-alcohol related hospitalisation (n=9,053)*: males (cont.)

	d) emergency admission and CVD condition				e) non-emergency admission and non-CVD condition				f) non-emergency admission and CVD condition			
Covariate	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***
Time spline1	0.040	0.015	0.065	*0.002*	-0.026	-0.048	-0.004	*0.021*	-0.093	-0.123	-0.064	*<0.001*
Time spline2	-0.060	-0.107	-0.013	*0.013*	0.027	-0.017	0.072	*0.229*	0.146	0.088	0.205	*<0.001*
Age at first event	0.013	0.011	0.016	*<0.001*	-0.005	-0.007	-0.002	*<0.001*	0.011	0.008	0.013	*<0.001*
SIMD (ref.=most deprived)												
2nd	-0.120	-0.267	0.026	*0.108*	0.197	0.078	0.317	*0.001*	-0.092	-0.208	0.024	*0.121*
3rd	-0.093	-0.241	0.056	*0.220*	0.099	-0.003	0.201	*0.058*	0.085	-0.037	0.207	*0.173*
4th	-0.157	-0.311	-0.004	*0.044*	0.217	0.103	0.332	*<0.001*	-0.058	-0.180	0.065	*0.355*
5th(least deprived)	-0.309	-0.481	-0.136	*<0.001*	0.372	0.213	0.531	*<0.001*	-0.074	-0.218	0.070	*0.316*
Constant	-2.592	-2.792	-2.393	*<0.001*	0.358	0.179	0.537	*<0.001*	-1.744	-1.933	-1.555	*<0.001*

Table 7-8 Modelling the risk of 6 subsequent events *following non-alcohol related hospitalisation (n=11,666)*: females

	a) wholly alcohol-related hospitalisation				b) partly alcohol-related hospitalisation				c) emergency admission and non-CVD condition			
Covariate	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***
Time spline1	-0.055	-0.128	0.018	*0.143*	0.033	-0.004	0.069	*0.081*	0.041	0.026	0.055	*<0.001*
Time spline2	0.110	-0.030	0.249	*0.123*	-0.036	-0.100	0.029	*0.278*	-0.059	-0.086	-0.033	*<0.001*
Age at first event	-0.016	-0.021	-0.010	*<0.001*	0.003	-0.0002	0.006	*0.071*	-0.002	-0.004	-0.001	*0.002*
SIMD (ref.=most deprived)												
2nd	-0.116	-0.414	0.182	*0.446*	0.079	-0.104	0.262	*0.396*	-0.021	-0.082	0.040	*0.503*
3rd	-0.090	-0.434	0.253	*0.607*	0.071	-0.086	0.229	*0.376*	-0.065	-0.134	0.003	*0.061*
4th	-0.156	-0.465	0.152	*0.320*	0.154	-0.016	0.323	*0.077*	-0.097	-0.167	-0.028	*0.006*
5th(least deprived)	0.072	-0.349	0.494	*0.737*	0.076	-0.102	0.255	*0.403*	-0.159	-0.245	-0.074	*<0.001*
Constant	-1.684	-2.032	-1.337	*<0.001*	-1.789	-2.023	-1.554	*<0.001*	-0.562	-0.664	-0.461	*<0.001*

Table 7-8 Modelling the risk of 6 subsequent events *following non-alcohol related hospitalisation (n=11,666)*: females (cont.)

	d) emergency admission and CVD condition				e) non-emergency admission and non-CVD condition				f) non-emergency admission and CVD condition			
Covariate	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***
Time spline1	0.039	0.015	0.064	*0.001*	-0.036	-0.053	-0.020	*<0.001*	-0.052	-0.083	-0.020	*0.001*
Time spline2	-0.037	-0.083	0.008	*0.111*	0.039	0.009	0.070	*0.010*	0.111	0.052	0.171	*<0.001*
Age at first event	0.018	0.016	0.020	*<0.001*	-0.004	-0.006	-0.003	*<0.001*	0.019	0.017	0.021	*<0.001*
SIMD (ref.=most deprived)												
2nd	-0.066	-0.166	0.034	*0.197*	0.026	-0.045	0.097	*0.472*	-0.108	-0.220	0.005	*0.060*
3rd	-0.024	-0.121	0.073	*0.629*	0.053	-0.024	0.129	*0.177*	-0.080	-0.204	0.043	*0.202*
4th	-0.029	-0.134	0.076	*0.590*	0.057	-0.024	0.137	*0.167*	-0.109	-0.244	0.026	*0.112*
5th(least deprived)	-0.216	-0.340	-0.091	*0.001*	0.145	0.045	0.244	*0.004*	-0.060	-0.206	0.085	*0.416*
Constant	-3.163	-3.342	-2.984	*<0.001*	0.546	0.434	0.658	*<0.001*	-2.711	-2.908	-2.514	*<0.001*

Table 7-9 Time spline variable of modelling the risk of subsequent events *following non-alcohol related hospitalisation*

Cycle (year)	Time spline1	Time spline2	Cycle (year)	Time spline1	Time spline2	Cycle (year)	Time spline1	Time spline2
1	1	0	35	35	24.0003	68	68	51.0009
2	2	0.00826	36	36	24.8185	69	69	51.8191
3	3	0.06612	37	37	25.6367	70	70	52.6373
4	4	0.22314	38	38	26.4549	71	71	53.4555
5	5	0.51756	39	39	27.2731	72	72	54.2737
6	6	0.94215	40	40	28.0913	73	73	55.0919
7	7	1.47831	41	41	28.9095	74	74	55.9101
8	8	2.10744	42	42	29.7277	75	75	56.7283
9	9	2.81095	43	43	30.5459	76	76	57.5465
10	10	3.57025	44	44	31.3641	77	77	58.3647
11	11	4.36674	45	45	32.1823	78	78	59.1829
12	12	5.18182	46	46	33.0005	79	79	60.0011
13	13	6	47	47	33.8187	80	80	60.8193
14	14	6.81818	48	48	34.6369	81	81	61.6375
15	15	7.63636	49	49	35.4551	82	82	62.4557
16	16	8.45455	50	50	36.2733	83	83	63.2739
17	17	9.27273	51	51	37.0915	84	84	64.0921
18	18	10.0909	52	52	37.9097	85	85	64.9103
19	19	10.9091	53	53	38.7279	86	86	65.7285
20	20	11.7273	54	54	39.5461	87	87	66.5467
21	21	12.5455	55	55	40.3643	88	88	67.3649
22	22	13.3637	56	56	41.1825	89	89	68.1831
23	23	14.1819	57	57	42.0007	90	90	69.0013
24	24	15.0001	58	58	42.8189	91	91	69.8195
25	25	15.8183	59	59	43.6371	92	92	70.6377
26	26	16.6365	60	60	44.4553	93	93	71.4559
27	27	17.4547	61	61	45.2735	94	94	72.2741
28	28	18.2729	62	62	46.0917	95	95	73.0923
29	29	19.0911	63	63	46.9099	96	96	73.9105
30	30	19.9093	64	64	47.7281	97	97	74.7287
31	31	20.7275	65	65	48.5463	98	98	75.5469
32	32	21.5457	66	66	49.3645	99	99	76.3651
33	33	22.3639	67	67	50.1827	100	100	77.1833
34	34	23.1821						

7.3.3 Using the alcohol intervention model to predict subsequent hospitalisations and reduction of HRQoL

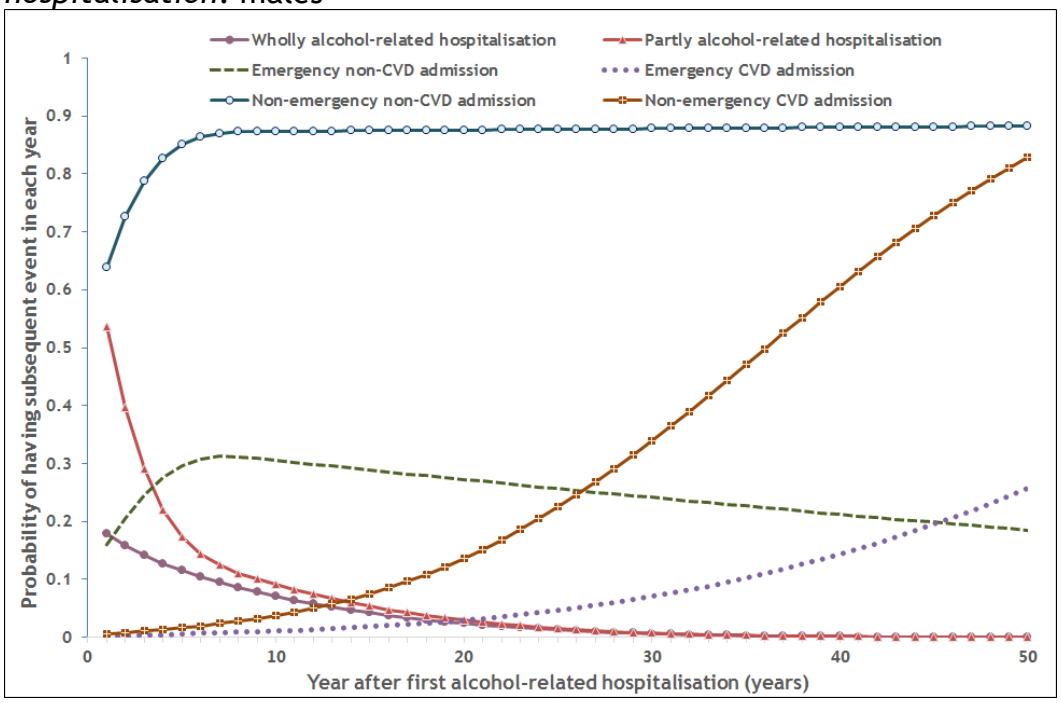
When using the alcohol intervention model to predict the risks of six hospitalisations following first alcohol-related and non-alcohol related hospitalisations, modifiable risk factors were defined and classified by gender and the first hospitalisation conditions as shown in Figure 7-14 and Figure 7-16 for males following alcohol-related and non-alcohol related conditions, respectively. Figure 7-15 and Figure 7-17 show the predicted risks of those events for females following alcohol-related and non-alcohol related conditions, respectively. The selected risk profiles for males were aged 30 years, AUDIT score = 10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior hospitalisation over the last year, and best GHQ score. For females, the selected risk profiles were aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, prior hospitalisation over the last year, and best GHQ score. This prediction assumed that the first event occurred immediately in the first year of entering the model based on the suggestion from (Holmes et al., 2012)).

In the same way as the observed data, the predicted risks of subsequent events post alcohol-related hospitalisation were changeable over time, while the risks of these events post non-alcohol related hospitalisation were more reliable. When comparing between the two types of hospitalisations, alcohol-related hospitalised patients were found to be higher risk of subsequent events. The probability of subsequent non-emergency and non-CVD admission was found the highest risk followed by emergency and non-CVD hospitalisation both men and women. After the first alcohol-related hospitalisation, the risks of subsequent wholly and partly alcohol-related events were high after the year of incurring the first event and fell dramatically during the first five years. On the contrary, the probability of having CVD hospitalisation (emergency and non-emergency admissions) was very low during the first 10-years and rose gradually after that. Following non-alcohol related hospitalisation, the risks of having six

subsequent events remained steady over the lifetime, and the risk of CVD hospitalisation showed a slight increase 20-years after the first admission.

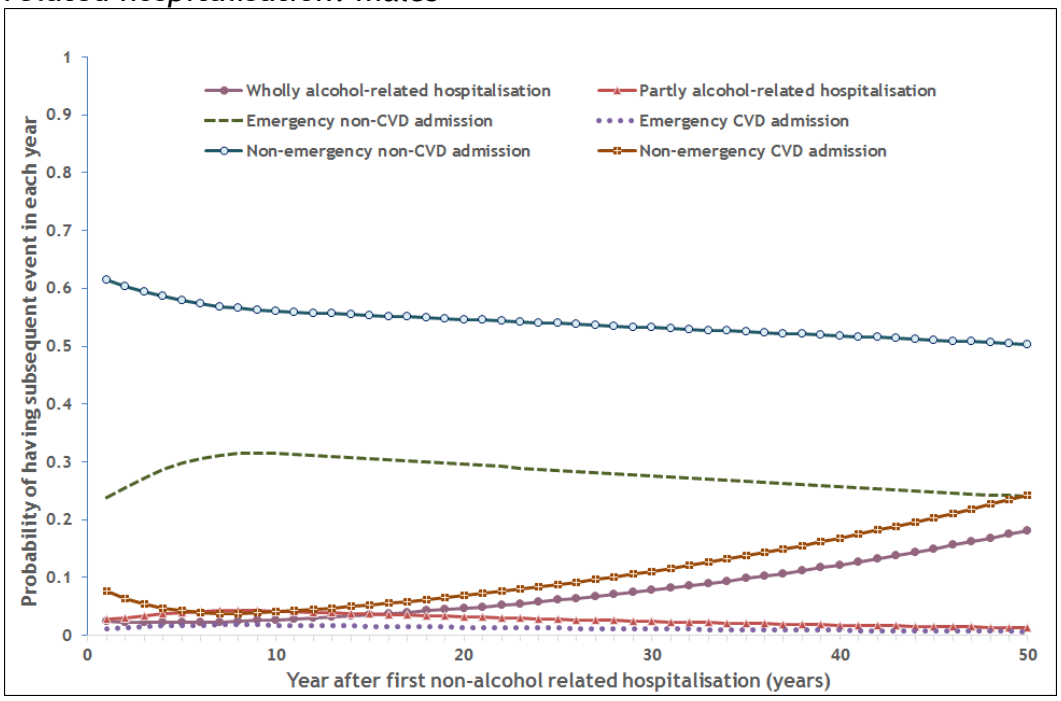
Figure 7-18 to Figure 7-21 illustrate the predicted utility decrement of the 6 hospitalisations following alcohol-related and non-alcohol related events, of which Figure 7-18 and Figure 7-19 are for males and Figure 7-20 and Figure 7-21 are for females. The scenarios of risk profiles and first events were the same as described in the risk prediction scenario above. The predicting effect of subsequent events on HRQoL was estimated from the risks of each event weighted by the associated utility decrement. As can be seen from these graphs compared with the predicted risks graphs (Figure 7-14 to Figure 7-17), similar trends were observed for each of the six events with different magnitudes, depending on the utility decrement of each event. For post alcohol-related hospitalisation, a very high effect on HRQoL during the five years after the first event was seen following a wholly alcohol-related hospitalisation, and females were more affected than males. Moreover, readmission with CVD condition affected the HRQoL more than the non-CVD condition for both post alcohol-related and non-alcohol related event so the predicted utility decrement of subsequent CVD hospitalisation was higher than non-CVD condition for both males and females. Furthermore, Figure 7-22 to Figure 7-25 show the predicted reduction of overall HRQoL due to hospitalisation and survival following alcohol-related and non-alcohol related conditions as classified by gender and first hospitalisation. From these graphs, the area under the survival curve but above the utility decrement area is summed to calculate the remaining QALY.

Figure 7-14 Predicted risk of 6 subsequent events *following alcohol related hospitalisation*: males*



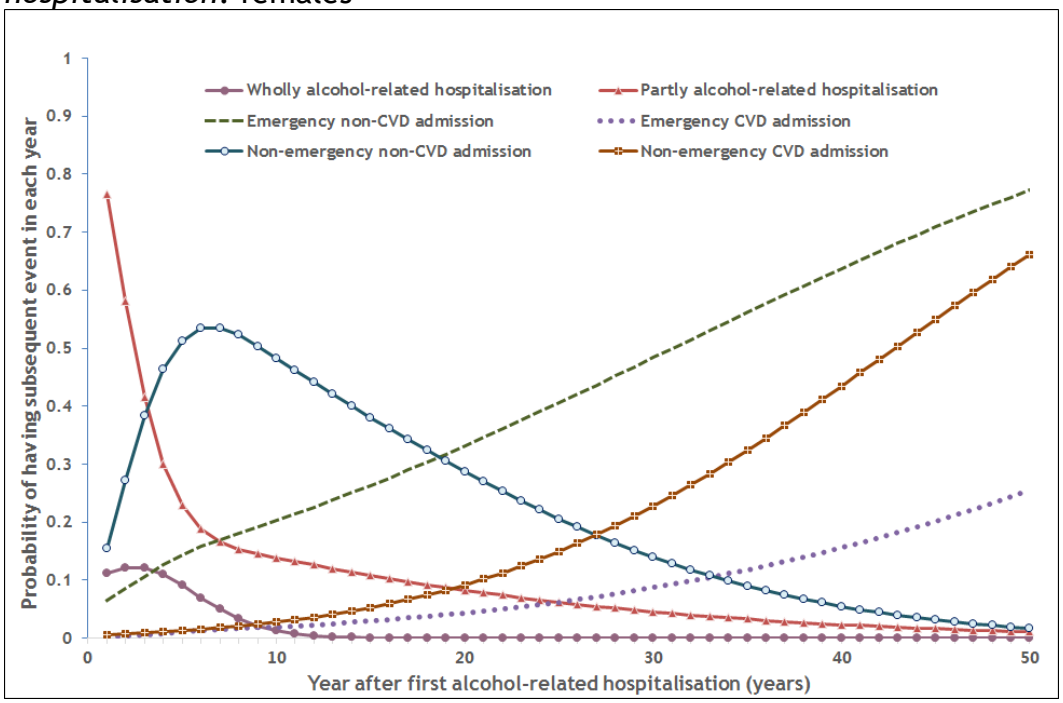
*Risk profiles: males, aged 30 years, AUDIT score=10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score. First event occurred at the same age.

Figure 7-15 Predicted risk of 6 subsequent events *following non-alcohol related hospitalisation*: males*



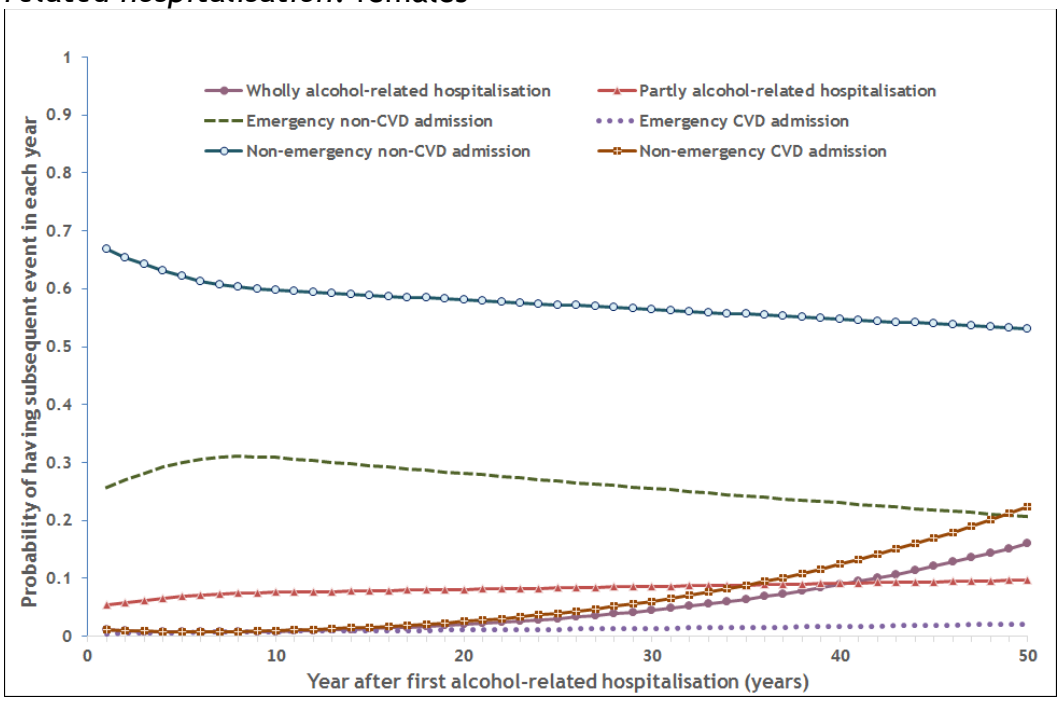
*Risk profiles: males, aged 30 years, AUDIT score=10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score. First event occurred at the same age.

Figure 7-16 Predicted risk of 6 subsequent events *following alcohol related hospitalisation*: females*



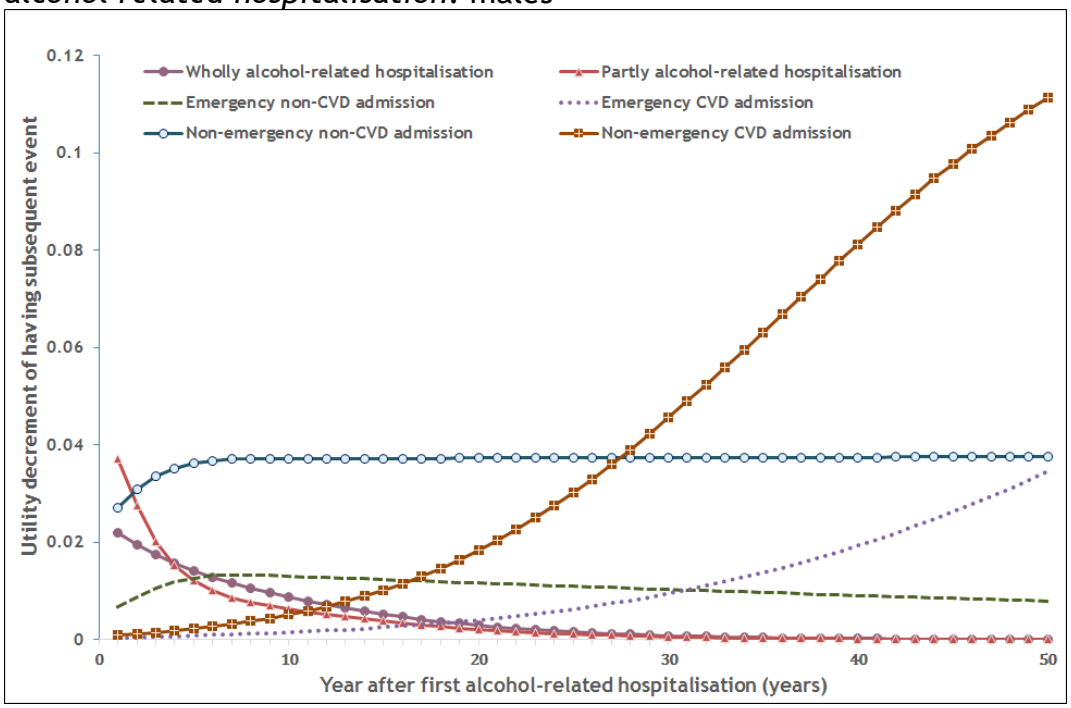
*Risk profiles: females, aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score. First event occurred at the same age.

Figure 7-17 Predicted risk of 6 subsequent events *following non-alcohol related hospitalisation*: females



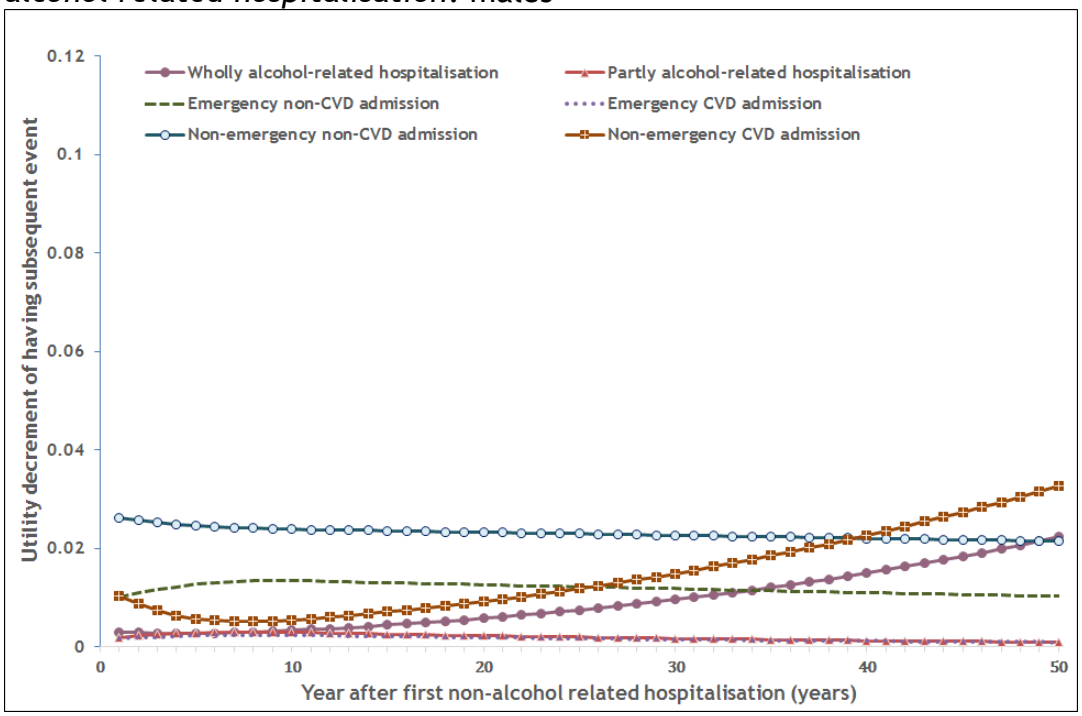
*Risk profiles: females, aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score. First event occurred at the same age.

Figure 7-18 Predicted utility decrement of 6 subsequent events *following alcohol related hospitalisation*: males*



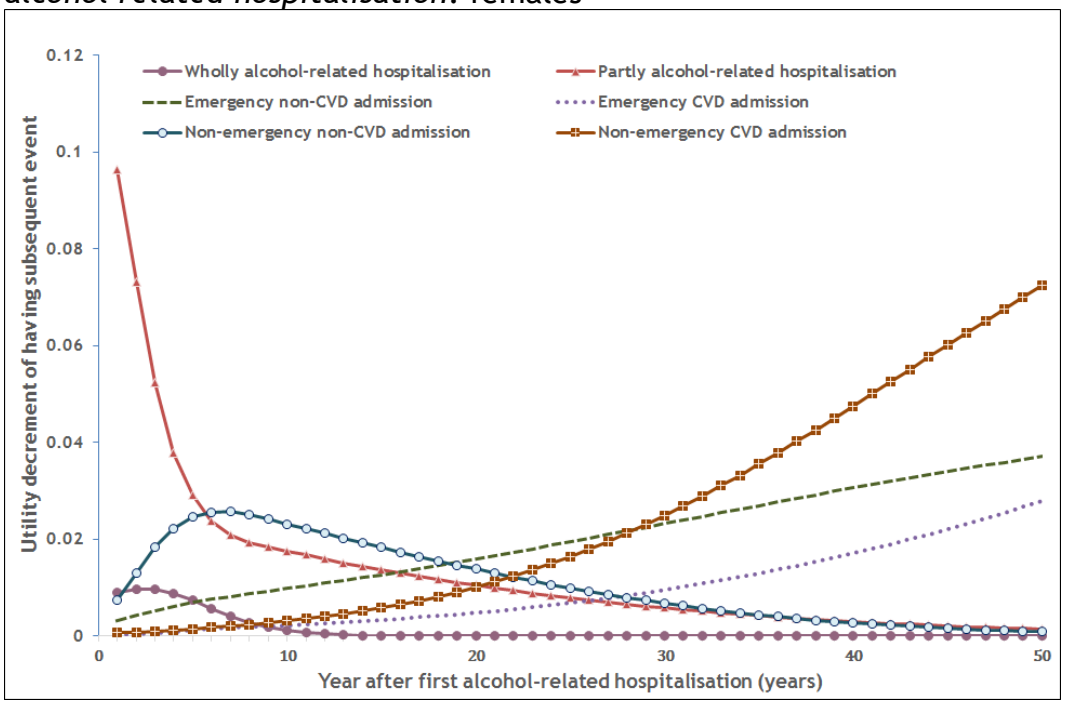
*Risk profiles: males, aged 30 years, AUDIT score=10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score. First event occurred at the same age.

Figure 7-19 Predicted utility decrement of 6 subsequent events *following non-alcohol related hospitalisation*: males*



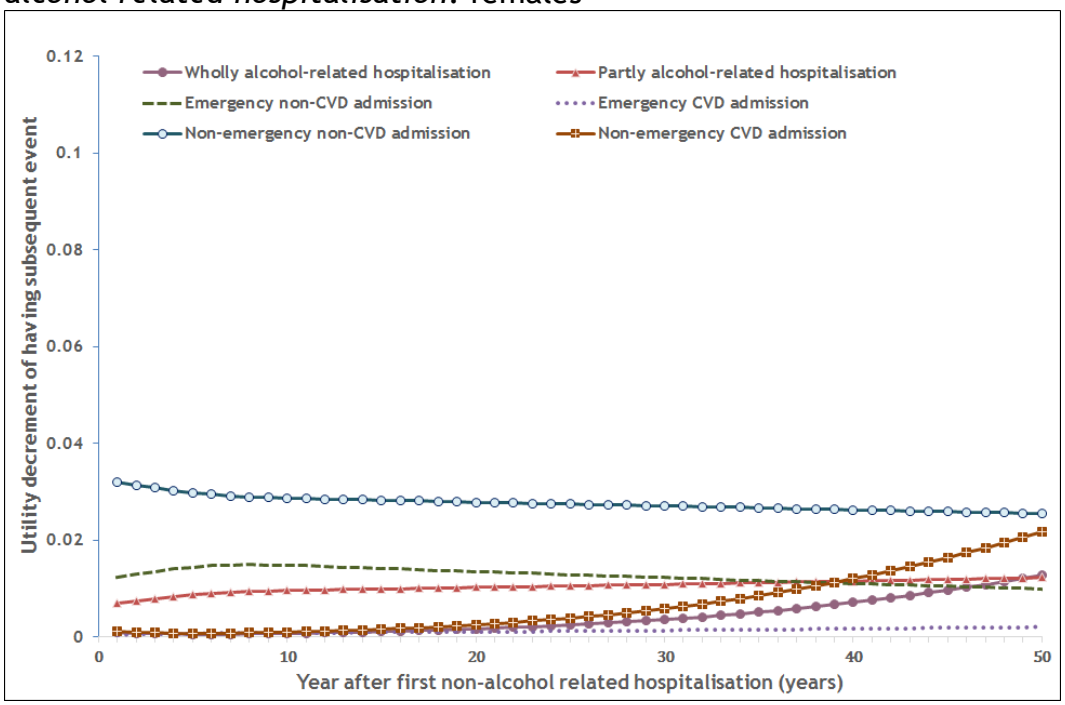
*Risk profiles: males, aged 30 years, AUDIT score=10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score. First event occurred at the same age.

Figure 7-20 Predicted utility decrement of 6 subsequent events *following alcohol related hospitalisation*: females*



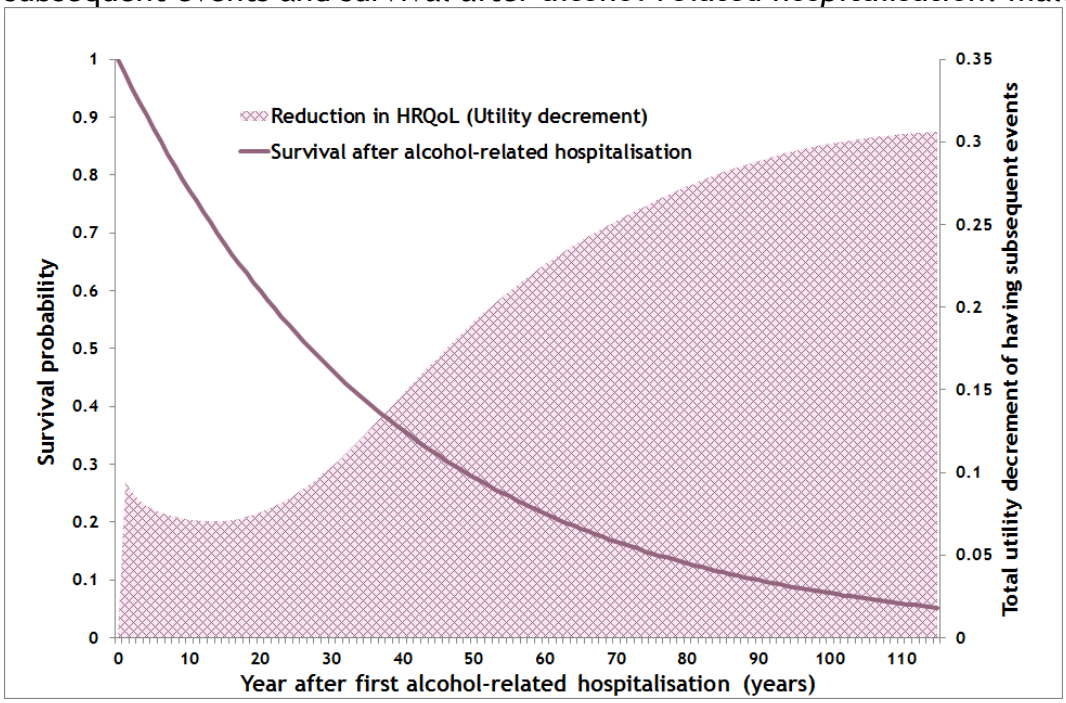
*Risk profiles: females, aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score. First event occurred at the same age.

Figure 7-21 Predicted utility decrement of 6 subsequent events *following non-alcohol related hospitalisation*: females



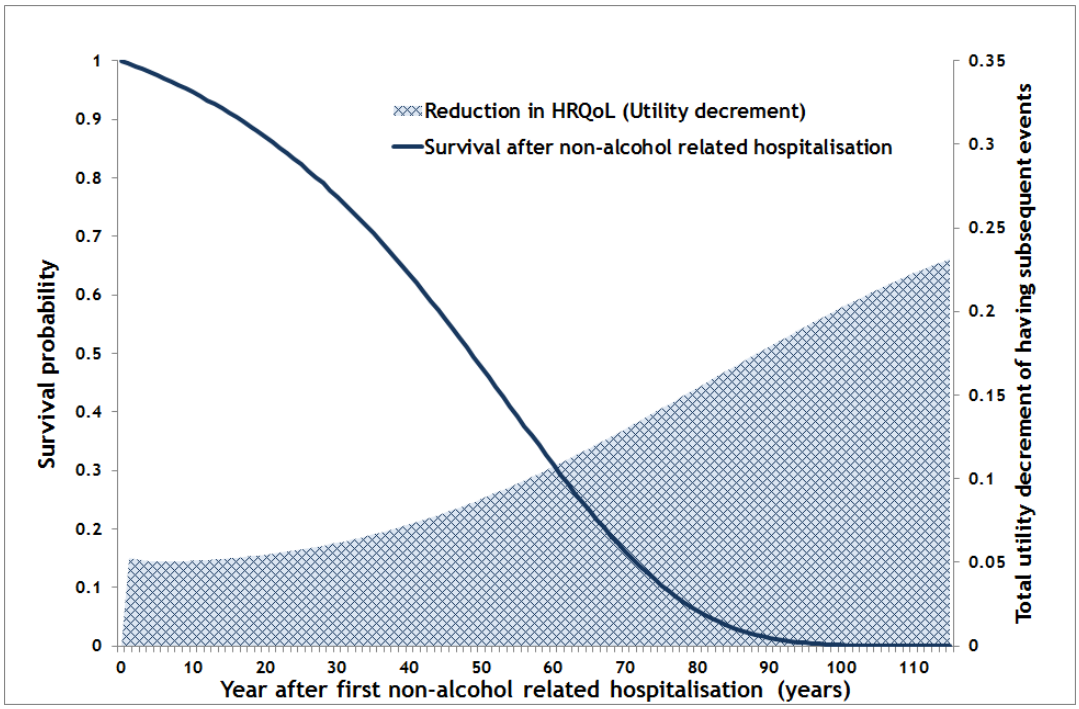
*Risk profiles: females, aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score. First event occurred at the same age.

Figure 7-22 Predicted reduction in HRQoL (utility decrement) due to subsequent events and survival after *alcohol-related hospitalisation*: males*



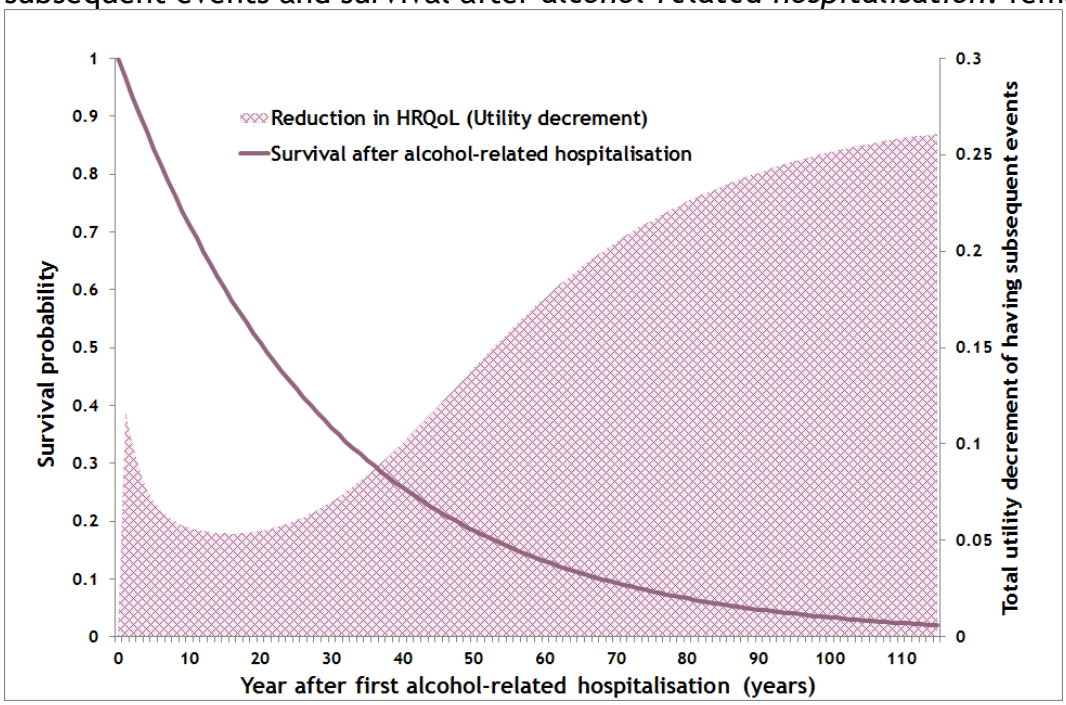
*Risk profiles: males, aged 30 years, AUDIT score=10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score. First event occurred at the same age.

Figure 7-23 Predicted reduction in HRQoL (utility decrement) due to subsequent events and survival after *non-alcohol related hospitalisation*: males*



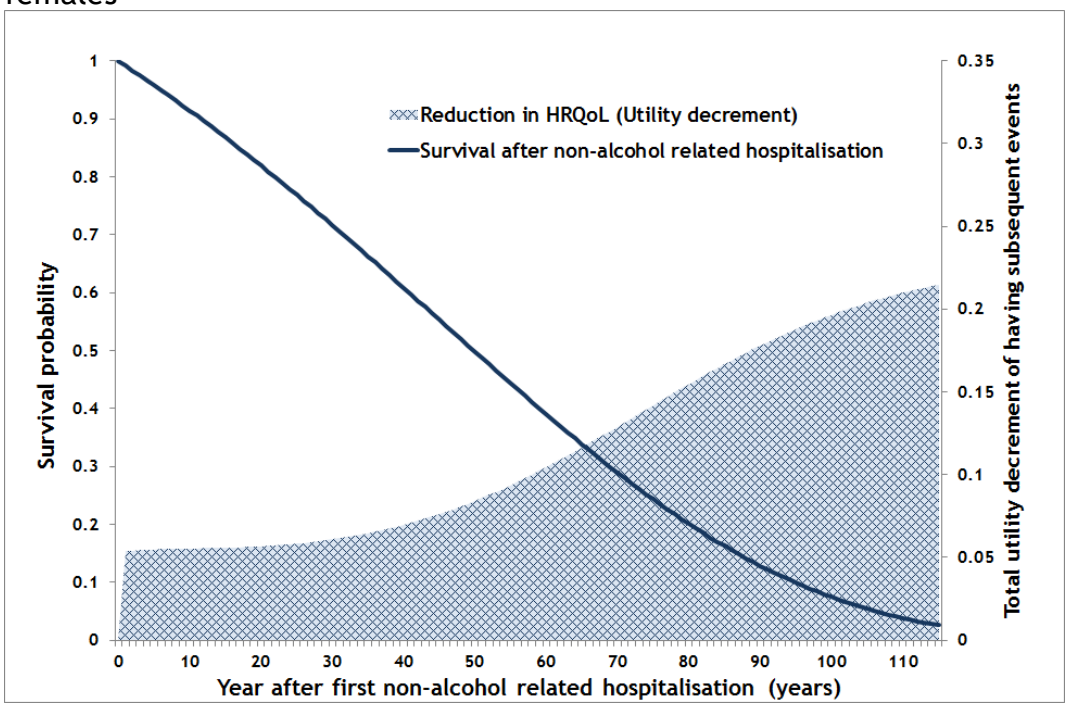
*Risk profiles: males, aged 30 years, AUDIT score=10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score. First event occurred at the same age.

Figure 7-24 Predicted reduction in HRQoL (utility decrement) due to subsequent events and survival after *alcohol-related hospitalisation*: females*



*Risk profiles: females, aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score. First event occurred at the same age.

Figure 7-25 Predicted reduction in HRQoL (utility decrement) due to subsequent events and survival after *non-alcohol related hospitalisation*: females*



*Risk profiles: females, aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score. First event occurred at the same age.

7.3.4 Estimating the remaining QALY

Table 7-10 and Table 7-11 a) to c) demonstrate the three stages of estimating the remaining QALYs after entering the model of individual risk profile for males and females aged 30 years, respectively. Table 7-10a and Table 7-11a represent the first stage which is the QALYs following first hospitalisations for 100 annual cycles. For example, if the individual risk profile of males aged 30 years had a wholly alcohol-related hospitalisation in the first year (first cycle) after the survey date, the remaining QALYs would then be 36.7 years. Table 7-10b and Table 7-11b show the probabilities of having eight first events across 100 yearly cycles derived from the cause specific hazard model of particular risk profiles as detailed in Chapter 6. Finally, the remaining QALYs of each health state (Table 7-10a and Table 7-11a) were weighted by the probabilities of having a particular event (Table 7-10b and Table 7-11b), and the predicted remaining QALYs after the survey date were calculated as shown in Table 7-10c and Table 7-11c. As a result, the estimated remaining QALYs of the defined risk profiles were 38.85 years and 40.11 years for males and females aged 30, respectively.

To demonstrate the use of the alcohol intervention model for predicting QALYs, the selected risk profiles were varied by age, smoking status and SIMD quintile. Then, the predicted remaining QALYs after entering the model of these risk profiles are illustrated in Table 7-12 and 7-13 for males and females, respectively. The alcohol intervention model shows its ability to discriminate between risk profiles as presented by the different remaining QALY for both males and females. The results revealed that higher-risk drinking (higher AUDIT score), more deprived status and current smoker resulted in less remaining QALYs when other related risk profiles were also changed based on the characteristics of the study population.

Table 7-10 Estimating quality adjusted life year (QALY) using 3 stages: males*

a) QALY remaining upon entering model (for hospitalisation, QALY is equal to time before event added by time remaining after event)

Cycle (years)	Wholly alcohol-related hospitalisation	Partly alcohol-related hospitalisation	Non-emergency non-CVD admission	Non-emergency CVD admission	Emergency non-CVD admission	Emergency CVD admission	Alcohol-related death	Non-alcohol related death
1	36.7	36.7	41.7	41.7	41.7	41.7	0.8	0.8
2	36.3	36.3	41.4	41.4	41.4	41.4	1.6	1.6
3	35.9	35.9	41.0	41.0	41.0	41.0	2.3	2.3
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
22	33.0	33.0	37.6	37.6	37.6	37.6	17.1	17.1
23	33.1	33.1	37.6	37.6	37.6	37.6	17.9	17.9
24	33.3	33.3	37.6	37.6	37.6	37.6	18.6	18.6
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
100	74.9	74.9	74.5	74.5	74.5	74.5	74.2	74.2

*Risk profiles: males, aged 30 years, AUDIT score=10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score

Table 7-10 Estimating quality adjusted life year (QALY) using 3 stages: males* (cont.)

b) Probability of having eight events over yearly 100 cycles

Cycle (years)	Wholly alcohol-related hospitalisation	Partly alcohol-related hospitalisation	Non-emergency non-CVD admission	Non-emergency CVD admission	Emergency non-CVD admission	Emergency CVD admission	Alcohol-related death	Non-alcohol related death
1	0.0012	0.0037	0.0674	0.0013	0.0343	0.0022	0.0003	0.0004
2	0.0011	0.0034	0.0582	0.0012	0.0299	0.0021	0.0003	0.0004
3	0.0009	0.0032	0.0504	0.0011	0.0261	0.0019	0.0003	0.0004
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
22	0.0001	0.0012	0.0047	0.0003	0.0028	0.0008	0.0001	0.0004
23	0.0001	0.0011	0.0042	0.0003	0.0025	0.0008	0.0001	0.0004
24	0.0001	0.0011	0.0037	0.0003	0.0023	0.0008	0.0001	0.0004
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
100	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

*Risk profiles: males, aged 30 years, AUDIT score=10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score

Table 7-10 Estimating quality adjusted life year (QALY) using 3 stages: males* (cont.)

c) Weighting remaining QALY estimated from stage a) multiplied by stage b)

Cycle (years)	Wholly alcohol-related hospitalisation	Partly alcohol-related hospitalisation	Non-emergency non-CVD admission	Non-emergency CVD admission	Emergency non-CVD admission	Emergency CVD admission	Alcohol-related death	Non-alcohol related death	***Sum***
1	0.0452	0.1345	2.8124	0.0529	1.4324	0.0924	0.0002	0.0003	4.5703
2	0.0384	0.1234	2.4089	0.0480	1.2364	0.0857	0.0005	0.0006	2.6187
3	0.0328	0.1136	2.0692	0.0437	1.0702	0.0797	0.0006	0.0009	2.2593
.	.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.	.
22	0.0026	0.0381	0.1766	0.0113	0.1057	0.0306	0.0015	0.0068	0.2286
23	0.0023	0.0367	0.1577	0.0107	0.0951	0.0295	0.0015	0.0072	0.2074
24	0.0021	0.0354	0.1409	0.0101	0.0857	0.0286	0.0015	0.0076	0.1885
.	.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.	.
100	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

*Risk profiles: males, aged 30 years, AUDIT score=10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score

Total QALY remaining (Cumulative sum over 100 cycles) = 38.85

Table 7-11 Estimating quality adjusted life year (QALY) using 3 stages: females*

a) QALY remaining upon entering model (for hospitalisation, QALY is equal to time before event added by time remaining after event)

Cycle (years)	Wholly alcohol-related hospitalisation	Partly alcohol-related hospitalisation	Non-emergency non-CVD admission	Non-emergency CVD admission	Emergency non-CVD admission	Emergency CVD admission	Alcohol-related death	Non-alcohol related death
1	28.5	28.5	45.5	45.5	45.5	45.5	0.8	0.8
2	28.1	28.1	44.9	44.9	44.9	44.9	1.6	1.6
3	27.8	27.8	44.3	44.3	44.3	44.3	2.4	2.4
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
22	27.9	27.9	36.8	36.8	36.8	36.8	17.1	17.1
23	28.1	28.1	36.7	36.7	36.7	36.7	17.9	17.9
24	28.5	28.5	36.6	36.6	36.6	36.6	18.7	18.7
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
100	73.9	73.9	73.8	73.8	73.8	73.8	73.4	73.4

*Risk profiles: females, aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score

Table 7-11 Estimating quality adjusted life year (QALY) using 3 stages: females* (cont.)

b) Probability of having eight events over yearly 100 cycles

Cycle (years)	Wholly alcohol-related hospitalisation	Partly alcohol-related hospitalisation	Non-emergency non-CVD admission	Non-emergency CVD admission	Emergency non-CVD admission	Emergency CVD admission	Alcohol-related death	Non-alcohol related death
1	0.0009	0.0070	0.0942	0.0008	0.0397	0.0009	0.0010	0.0004
2	0.0007	0.0061	0.0778	0.0007	0.0332	0.0008	0.0010	0.0004
3	0.0006	0.0054	0.0646	0.0006	0.0278	0.0007	0.0009	0.0004
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
22	0.0000	0.0009	0.0034	0.0000	0.0018	0.0002	0.0006	0.0003
23	0.0000	0.0008	0.0029	0.0000	0.0016	0.0002	0.0006	0.0003
24	0.0000	0.0007	0.0026	0.0000	0.0014	0.0002	0.0006	0.0003
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
100	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

*Risk profiles: females, aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score

Table 7-11 Estimating quality adjusted life year (QALY) using 3 stages: females* (cont.)

c) Weighting remaining QALY estimated from stage a) multiplied by stage b)

Cycle (years)	Wholly alcohol-related hospitalisation	Partly alcohol-related hospitalisation	Non-emergency non-CVD admission	Non-emergency CVD admission	Emergency non-CVD admission	Emergency CVD admission	Alcohol-related death	Non-alcohol related death	***Sum***
1	0.0250	0.1989	4.2874	0.0362	1.8066	0.0404	0.0008	0.0003	**6.3957**
2	0.0205	0.1722	3.4921	0.0297	1.4882	0.0356	0.0016	0.0006	**3.7145**
3	0.0169	0.1498	2.8570	0.0245	1.2314	0.0315	0.0022	0.0009	**3.0483**
.	.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.	.
22	0.0010	0.0239	0.1243	0.0013	0.0664	0.0062	0.0104	0.0055	**0.1505**
23	0.0009	0.0224	0.1082	0.0011	0.0584	0.0058	0.0109	0.0059	**0.1325**
24	0.0008	0.0209	0.0942	0.0010	0.0515	0.0055	0.0113	0.0062	**0.1169**
.	.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.	.
100	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	**0.0000**

*Risk profiles: females, aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score

Total QALY remaining (Cumulative sum over 100 cycles) = 40.11

Table 7-12 Predicted remaining QALY classified by risks profiles: males

AUDIT score	Smoker (5 CPD)					Non-smoker				
	Age 20 years					**Age 20 years**				
>20	34.07	39.11	42.61	43.70	45.54	34.15	39.10	42.61	43.75	45.58
16 - 19	38.11	43.01	46.73	48.10	50.08	38.16	43.02	46.75	48.14	50.15
8 - 15	39.10	43.99	47.77	49.19	51.21	39.15	44.00	47.78	49.23	51.24
0 - 7	41.06	45.95	49.81	51.33	53.46	41.11	45.96	49.83	51.40	53.49
	Age 30 years					**Age 30 years**				
>20	25.98	30.17	33.47	34.30	36.19	26.06	30.21	33.50	34.39	36.25
16 - 19	29.25	33.36	36.88	37.96	40.00	29.34	33.41	36.92	38.02	40.05
8 - 15	30.05	34.16	37.74	38.84	40.94	30.14	34.21	37.78	38.92	40.99
0 - 7	31.64	35.75	39.46	40.63	42.82	31.73	35.81	39.50	40.69	42.87
	Age 40 years					**Age 40 years**				
>20	19.00	22.42	25.28	25.92	27.64	19.08	22.47	25.34	26.00	27.73
16 - 19	21.53	24.94	28.02	28.82	30.70	21.61	24.99	28.08	28.89	30.80
8 - 15	22.16	25.56	28.69	29.54	31.46	22.23	25.61	28.77	29.61	31.56
0 - 7	23.40	26.80	30.06	30.95	32.98	23.47	26.87	30.12	31.03	33.05
	Age 50 years					**Age 50 years**				
>20	13.21	15.95	18.31	18.76	20.31	13.29	16.01	18.38	18.84	20.39
16 - 19	15.08	17.84	20.41	20.96	22.67	15.16	17.90	20.48	21.04	22.77
8 - 15	15.54	18.31	20.92	21.51	23.26	15.62	18.38	20.99	21.59	23.34
0 - 7	16.47	19.25	21.97	22.59	24.43	16.55	19.31	22.04	22.67	24.52
	1	2	3	4	5	1	2	3	4	5
	most deprived				**least deprived**	**most deprived**				**least deprived**
	SIMD quintile									

Note: binge drinking, BMI, physical activity, CVD, diabetes, prior hospitalisation, and GHQ score were varied but not presented.

Table 7-13 Predicted remaining QALY classified by risks profiles: females

AUDIT score	Smoker (4 CPD)					Non-smoker				
	Age 20 years					Age 20 years				
>17	38.64	44.47	46.55	49.24	53.02	38.68	44.56	46.66	49.32	53.12
13 - 16	41.29	47.81	50.01	52.61	56.99	41.29	47.84	50.05	52.65	57.05
5 - 12	42.35	49.14	51.38	53.99	58.58	42.35	49.17	51.43	53.98	58.59
0 - 4	43.42	50.42	52.71	55.29	60.10	43.39	50.44	52.74	55.27	60.12
	Age 30 years					Age 30 years				
>17	27.77	33.42	35.35	37.74	41.58	27.84	33.53	35.48	37.86	41.71
13 - 16	29.77	36.05	38.08	40.41	44.85	29.82	36.11	38.18	40.49	44.92
5 - 12	30.58	37.09	39.16	41.50	46.13	30.62	37.16	39.25	41.54	46.20
0 - 4	31.36	38.09	40.21	42.50	47.38	31.40	38.15	40.28	42.55	47.41
	Age 40 years					Age 40 years				
>17	19.02	23.57	25.13	27.06	30.41	19.11	23.71	25.29	27.19	30.57
13 - 16	20.47	25.52	27.17	29.07	32.95	20.55	25.64	27.30	29.17	33.07
5 - 12	21.05	26.29	27.97	29.83	33.94	21.13	26.40	28.09	29.95	34.03
0 - 4	21.61	27.03	28.74	30.59	34.87	21.67	27.13	28.83	30.67	34.95
	Age 50 years					Age 50 years				
>17	12.55	15.94	17.21	18.62	21.12	12.67	16.10	17.37	18.78	21.32
13 - 16	13.57	17.35	18.67	20.05	22.99	13.66	17.47	18.81	20.19	23.15
5 - 12	13.97	17.89	19.24	20.59	23.71	14.06	18.01	19.37	20.74	23.84
0 - 4	14.33	18.38	19.76	21.11	24.38	14.42	18.51	19.88	21.24	24.50
	1	2	3	4	5	1	2	3	4	5
	most deprived				least deprived	most deprived				least deprived
	SIMD quintile									

Note: binge drinking, BMI, physical activity, CVD, diabetes, prior hospitalisation, and GHQ score were varied but not presented.

7.4 Results: Modelling for predicting lifetime hospitalisation costs

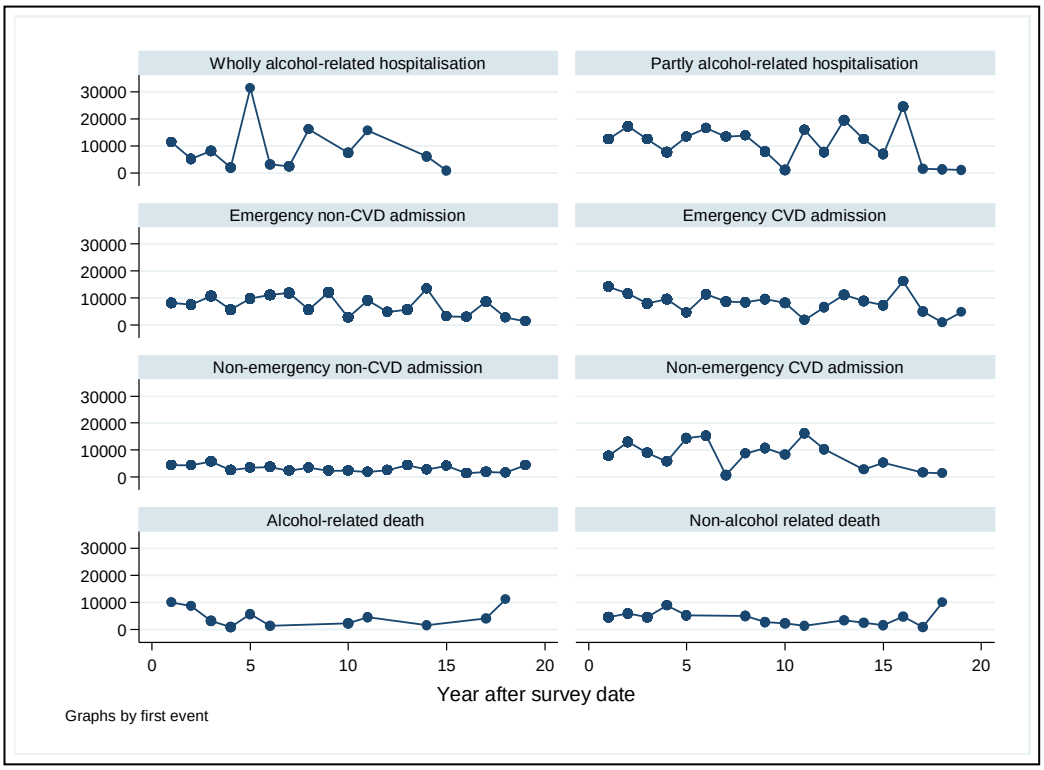
7.4.1 Estimated annual hospitalisation costs in the year of having the first event

Figure 7-26 and Figure 7-27 illustrate the graphs of observed mean annual hospitalisation costs in the year of having the first event during a 20-year follow up period for males and females, respectively. Almost all the observed first event costs are unstable except non-emergency admission with non-CVD condition, which is stable over the follow-up period for both males and females. The annual costs of alcohol-related hospitalisation were higher than non-alcohol related hospitalisation. The modelled annual hospitalisation costs in the year of having first hospitalisations were separated by gender, and the results are shown from Table 7-14 to Table 7-17 where the restricted cubic spline of time since the survey date are represented in Table 7-18. These modelling costs were performed particularly for SHeS cohorts who experienced the first hospitalisation after the survey date. As shown by the estimated coefficients of each first event costs, the results were different between men and women, which could support the justification of having separate models. Moreover, there were annual hospitalisation cost models where the age at survey date coefficient was statistically significant, whereas time spline and SIMD were not likely statistical significant for hospitalisation cost models.

The alcohol intervention model was used to predict healthcare costs of first alcohol-related and non-alcohol related events in each year after survey date, and the annual costs was adjusted by the annual risks of each event. The predicted mean of annual hospitalisation costs in the year of having first hospitalisation are presented in Figure 7-28 and Figure 7-29 for males and females, respectively. The selected risk profiles were defined for males, i.e. aged 30 years, AUDIT score=10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior

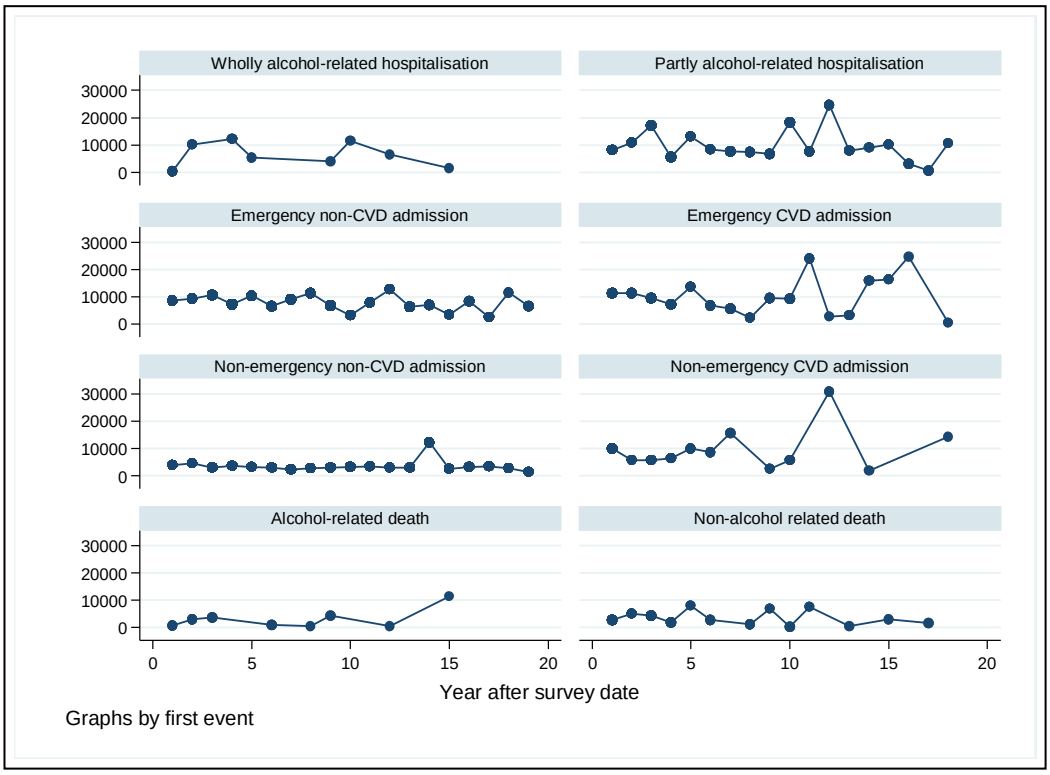
hospitalisation over last year, and best GHQ score. For females, the selected risk profiles were aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score. It can be clearly seen that the predicted annual healthcare costs plateau over time, and the costs for males are higher than females with different costs of alcohol-related and non-alcohol related hospitalisations. For males, the predicted annual costs of partly alcohol-related hospitalisation were found to be the highest costs followed by the predicted costs of emergency and non-emergency admission with CVD condition, and wholly alcohol-related hospitalisation. For females, the highest annual hospitalisation costs were wholly alcohol-related hospitalisation followed by emergency admission with and without CVD condition, and non-emergency admission without CVD condition.

Figure 7-26 Observed mean annual hospitalisation cost in the year of having first event: males



*Cost of death event derived from hospitalised patient and died within 28 days.

Figure 7-27 Observed mean annual hospitalisation cost in the year of having first event: females



*Cost of death event derived from hospitalised patient and died within 28 days.

Table 7-14 Modelling annual hospitalisation costs in year of having first *alcohol-related hospitalisation and death*: males

	a) wholly alcohol-related hospitalisation				b) partly alcohol-related hospitalisation				c) alcohol-related death			
Covariate*	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***
Time spline1	0.256	-0.133	0.645	0.196	0.087	-0.051	0.226	0.216	-0.627	-1.184	-0.070	0.027
Time spline2	-0.598	-1.392	0.195	0.140	-0.131	-0.407	0.145	0.353	1.142	0.147	2.136	0.024
Age at survey date	0.020	-0.006	0.046	0.136	0.010	-0.003	0.022	0.137	-0.035	-0.082	0.012	0.148
SIMD (ref.=most deprived)												
2nd	-0.294	-1.220	0.633	0.534	-0.689	-1.143	-0.234	0.003	-0.423	-1.389	0.544	0.391
3rd	-0.095	-1.045	0.855	0.844	-0.478	-0.901	-0.055	0.027	-0.316	-1.333	0.701	0.542
4th	0.128	-0.966	1.223	0.818	0.061	-0.452	0.574	0.816	-1.322	-3.002	0.359	0.123
5th(least deprived)	0.352	-0.871	1.576	0.572	-0.208	-0.727	0.311	0.432	0.901	-0.773	2.576	0.291
Constant	7.538	5.859	9.217	<0.001	8.772	7.839	9.706	<0.001	11.699	8.063	15.335	<0.001

*Covariates were derived from generalised linear model using gamma family with log link function.

Table 7-15 Modelling annual hospitalisation costs in year of having first *non-alcohol related hospitalisation and death*: males

	a) emergency admission and non-CVD condition				b) emergency admission and CVD condition				c) non-emergency admission and non-CVD condition			
Covariate*	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***
Time spline1	0.026	-0.068	0.120	0.591	-0.094	-0.226	0.037	0.161	-0.073	-0.148	0.003	0.059
Time spline2	-0.049	-0.244	0.146	0.623	0.208	-0.075	0.491	0.149	0.168	-0.010	0.345	0.064
Age at survey date	0.028	0.023	0.033	<0.001	0.020	0.008	0.032	0.001	0.016	0.010	0.021	<0.001
SIMD (ref.=most deprived)												
2nd	0.047	-0.275	0.369	0.776	0.271	-0.128	0.670	0.183	0.071	-0.144	0.287	0.516
3rd	-0.294	-0.556	-0.033	0.027	0.142	-0.237	0.522	0.462	0.053	-0.200	0.307	0.682
4th	0.012	-0.294	0.319	0.938	0.264	-0.132	0.659	0.192	0.222	-0.099	0.544	0.175
5th(least deprived)	-0.190	-0.485	0.104	0.206	-0.170	-0.577	0.238	0.414	0.035	-0.183	0.253	0.751
Constant	7.323	7.007	7.639	<0.001	7.862	6.964	8.759	<0.001	7.339	6.933	7.745	<0.001

*Covariates were derived from generalised linear model using gamma family with log link function.

Table 7-15 Modelling annual hospitalisation costs in year of having first *non-alcohol related hospitalisation and death*: males (cont.)

	d) non-emergency admission and CVD condition				e) non-alcohol related death			
Covariate*	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***
Time spline1	0.105	-0.053	0.264	0.192	0.495	0.017	0.973	0.042
Time spline2	-0.239	-0.576	0.099	0.166	-0.900	-1.802	0.002	0.051
Age at survey date	0.011	-0.006	0.027	0.197	0.011	-0.033	0.055	0.632
SIMD (ref.=most deprived)								
2nd	0.230	-0.313	0.773	0.406	-0.147	-1.345	1.051	0.810
3rd	0.662	0.157	1.168	0.010	-0.152	-1.330	1.027	0.801
4th	0.081	-0.368	0.530	0.722	-1.477	-3.174	0.219	0.088
5th(least deprived)	0.154	-0.354	0.663	0.552	0.427	-0.775	1.628	0.487
Constant	7.784	6.671	8.897	<0.001	6.022	2.902	9.142	<0.001

*Covariates were derived from generalised linear model using gamma family with log link function.

Table 7-16 Modelling annual hospitalisation costs in year of having first *alcohol-related hospitalisation and death*: females

	a) wholly alcohol-related hospitalisation				b) partly alcohol-related hospitalisation				c) alcohol-related death			
Covariate*	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***
Time spline1	0.008	-0.366	0.383	0.965	0.182	0.079	0.286	0.001	-0.199	-0.863	0.466	0.558
Time spline2	-0.038	-0.927	0.851	0.934	-0.313	-0.525	-0.100	0.004	0.428	-0.902	1.758	0.528
Age at survey date	0.032	0.006	0.057	0.015	0.023	0.015	0.030	<0.001	-0.023	-0.069	0.023	0.328
SIMD (ref.=most deprived)												
2nd	-0.073	-0.954	0.808	0.871	0.234	-0.090	0.557	0.157	0.081	-1.193	1.355	0.901
3rd	-0.140	-1.027	0.748	0.758	0.049	-0.247	0.344	0.747	-0.115	-1.409	1.179	0.862
4th	0.005	-1.228	1.238	0.993	0.319	-0.130	0.769	0.164	0.178	-1.630	1.986	0.847
5th(least deprived)	-0.364	-1.356	0.629	0.473	0.197	-0.154	0.549	0.272	0.077	-1.906	2.059	0.939
Constant	7.524	5.970	9.077	<0.001	7.029	6.526	7.533	<0.001	9.350	6.053	12.647	<0.001

*Covariates were derived from generalised linear model using gamma family with log link function.

Table 7-17 Modelling annual hospitalisation costs in year of having first *non-alcohol related hospitalisation and death*: females

	a) emergency admission and non-CVD condition				b) emergency admission and CVD condition				c) non-emergency admission and non-CVD condition			
Covariate*	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***
Time spline1	-0.016	-0.091	0.059	0.678	-0.035	-0.180	0.111	0.641	-0.089	-0.146	-0.033	0.002
Time spline2	0.029	-0.126	0.185	0.713	0.111	-0.194	0.417	0.475	0.191	0.053	0.329	0.007
Age at survey date	0.025	0.021	0.028	<0.001	0.030	0.018	0.042	<0.001	0.021	0.018	0.024	<0.001
SIMD (ref.=most deprived)												
2nd	0.185	-0.014	0.385	0.068	-0.366	-0.740	0.009	0.055	-0.050	-0.225	0.125	0.574
3rd	0.180	-0.091	0.451	0.192	-0.142	-0.580	0.296	0.525	-0.097	-0.270	0.075	0.268
4th	0.163	-0.057	0.382	0.146	-0.469	-0.840	-0.098	0.013	0.006	-0.211	0.222	0.960
5th(least deprived)	-0.088	-0.286	0.111	0.386	-0.055	-0.658	0.548	0.858	-0.090	-0.294	0.114	0.390
Constant	7.447	7.163	7.730	<0.001	7.309	6.412	8.207	<0.001	7.234	7.023	7.446	<0.001

*Covariates were derived from generalised linear model using gamma family with log link function.

Table 7-17 Modelling annual hospitalisation costs in year of having first *non-alcohol related hospitalisation and death*: females (cont.)

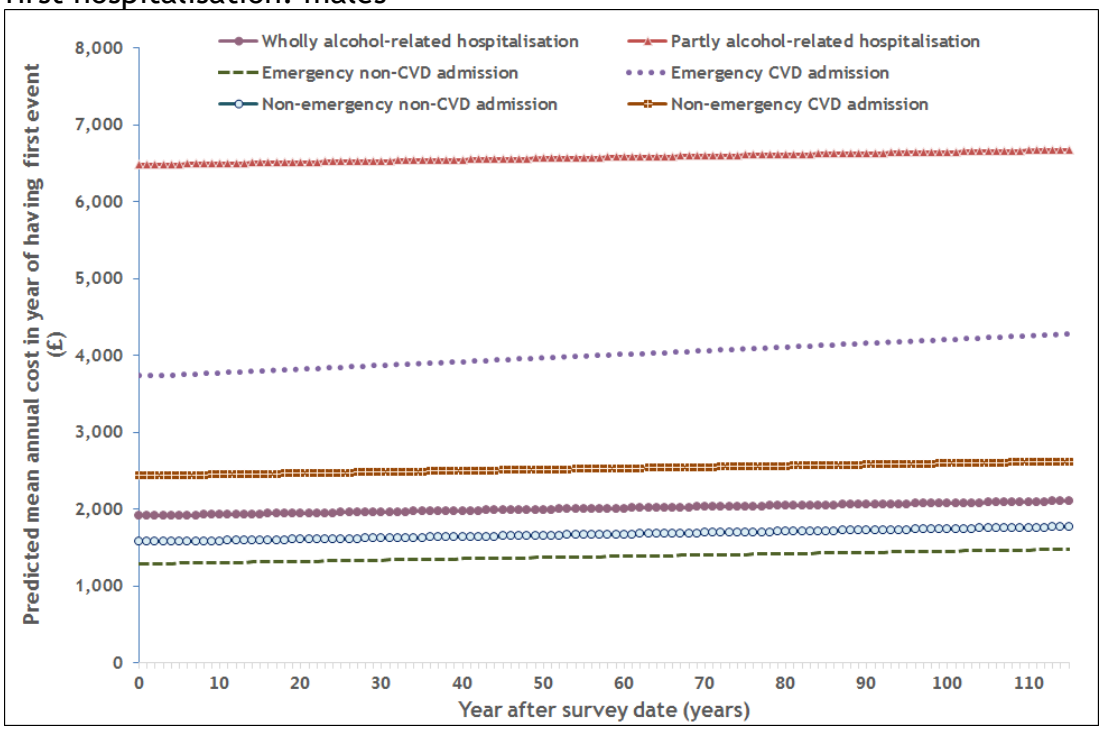
	d) non-emergency admission and CVD condition				e) non-alcohol related death			
Covariate*	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***
Time spline1	0.089	-0.120	0.298	0.405	0.264	-0.098	0.626	0.153
Time spline2	-0.097	-0.527	0.334	0.660	-0.516	-1.260	0.229	0.175
Age at survey date	0.054	0.029	0.079	<0.001	-0.028	-0.063	0.007	0.115
SIMD (ref.=most deprived)								
2nd	0.237	-0.370	0.845	0.444	-0.342	-1.348	0.664	0.506
3rd	0.273	-0.460	1.007	0.466	-0.087	-0.936	0.762	0.841
4th	0.039	-0.861	0.938	0.933	-0.416	-1.465	0.634	0.437
5th(least deprived)	0.750	-0.049	1.549	0.066	-0.132	-2.141	1.878	0.898
Constant	4.945	3.342	6.548	<0.001	8.926	6.415	11.437	<0.001

*Covariates were derived from generalised linear model using gamma family with log link function.

Table 7-18 Time spline variable of annual hospitalisation costs in year of having first event

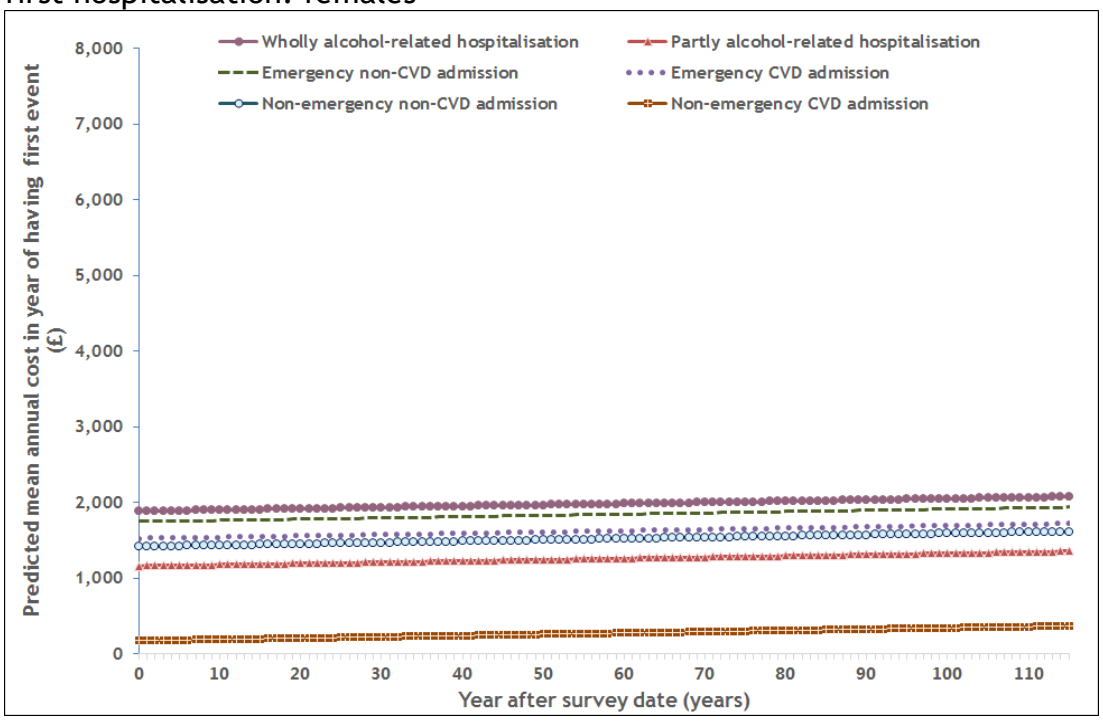
Cycle (year)	Time spline1	Time spline2	Cycle (year)	Time spline1	Time spline2	Cycle (year)	Time spline1	Time spline2
1	1	0	35	35	20.222	68	68	42.222
2	2	0.012	36	36	20.889	69	69	42.889
3	3	0.099	37	37	21.556	70	70	43.556
4	4	0.317	38	38	22.222	71	71	44.222
5	5	0.663	39	39	22.889	72	72	44.889
6	6	1.115	40	40	23.556	73	73	45.556
7	7	1.651	41	41	24.222	74	74	46.222
8	8	2.250	42	42	24.889	75	75	46.889
9	9	2.892	43	43	25.556	76	76	47.556
10	10	3.556	44	44	26.222	77	77	48.222
11	11	4.222	45	45	26.889	78	78	48.889
12	12	4.889	46	46	27.556	79	79	49.556
13	13	5.556	47	47	28.222	80	80	50.222
14	14	6.222	48	48	28.889	81	81	50.889
15	15	6.889	49	49	29.556	82	82	51.556
16	16	7.556	50	50	30.222	83	83	52.222
17	17	8.222	51	51	30.889	84	84	52.889
18	18	8.889	52	52	31.556	85	85	53.556
19	19	9.556	53	53	32.222	86	86	54.222
20	20	10.222	54	54	32.889	87	87	54.889
21	21	10.889	55	55	33.556	88	88	55.556
22	22	11.556	56	56	34.222	89	89	56.222
23	23	12.222	57	57	34.889	90	90	56.889
24	24	12.889	58	58	35.556	91	91	57.556
25	25	13.556	59	59	36.222	92	92	58.222
26	26	14.222	60	60	36.889	93	93	58.889
27	27	14.889	61	61	37.556	94	94	59.556
28	28	15.556	62	62	38.222	95	95	60.222
29	29	16.222	63	63	38.889	96	96	60.889
30	30	16.889	64	64	39.556	97	97	61.556
31	31	17.556	65	65	40.222	98	98	62.222
32	32	18.222	66	66	40.889	99	99	62.889
33	33	18.889	67	67	41.556	100	100	63.556
34	34	19.556						42.222

Figure 7-28 Predicted mean of annual hospitalisation cost in year of having first hospitalisation: males*



*Risk profiles: males, aged 30 years, AUDIT score=10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score.

Figure 7-29 Predicted mean of annual hospitalisation cost in year of having first hospitalisation: females*



*Risk profiles: females, aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score.

7.4.2 Estimated annual hospitalisation costs in following years after first event

Figure 7-30 and Figure 7-31 illustrate the observed mean of annual hospitalisation costs post-first hospitalisation during a 20-year follow-up period classified by gender and first hospitalisation (i.e. alcohol-related and non-alcohol related hospitalisations). For males, Figure 7-30 shows that the annual costs are approximately comparable between alcohol-related and non-alcohol related hospitalisations during the first 10 years, and then non-alcohol related hospitalisation is shown to be the higher afterwards. Figure 7-31 shows the annual costs for females which show that the trends of observed hospitalisation costs are similar to males with slightly lower costs.

Furthermore, the annual hospitalisation costs in following years after first hospitalisations were modelled and separated by gender and first hospitalisations. The model coefficients are reported in Table 7-19 for males and Table 7-20 for females where the restricted cubic spline of time since the first event was the same as Table 7-6 and Table 7-9 for the post alcohol-related event model and post non-alcohol related event model, respectively. As shown by the estimated coefficients of each cost model, the age at first event coefficient was reported to be statistically significant, particularly for the post non-alcohol related hospitalisation cost model for males. For females, the age at first event coefficient was statistically significant in both post alcohol-related and non-alcohol related hospitalisation cost models, whereas time spline was shown to be significant only in the post non-alcohol related hospitalisation cost model. Nevertheless, SIMD was not statistically significant for all cost models.

Afterwards, the model was used to predict annual healthcare costs in following years after first alcohol-related and non-alcohol related hospitalisations. The predicted mean of annual hospitalisation costs and survival following first hospitalisation are demonstrated from Figure 7-32 to

Figure 7-35, classified by gender and first hospitalisations. The selected risk profiles for males were aged 30 years, AUDIT score=10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score. For females, the selected risk profiles were aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score. This prediction assumed that the first event occurred immediately in the first year of entering the model based on the suggestion from (Holmes et al., 2012). For males, when comparing annual hospitalisation costs weighted by survival probability between post alcohol-related and post non-alcohol related admissions, the predicted costs of the post alcohol-related event was approximately 1.5 times higher. In contrast, for females, the predicted costs of post non-alcohol-related event was higher than the costs of post alcohol-related hospitalisation.

Figure 7-30 Observed mean annual hospitalisation cost post first hospitalisation: males

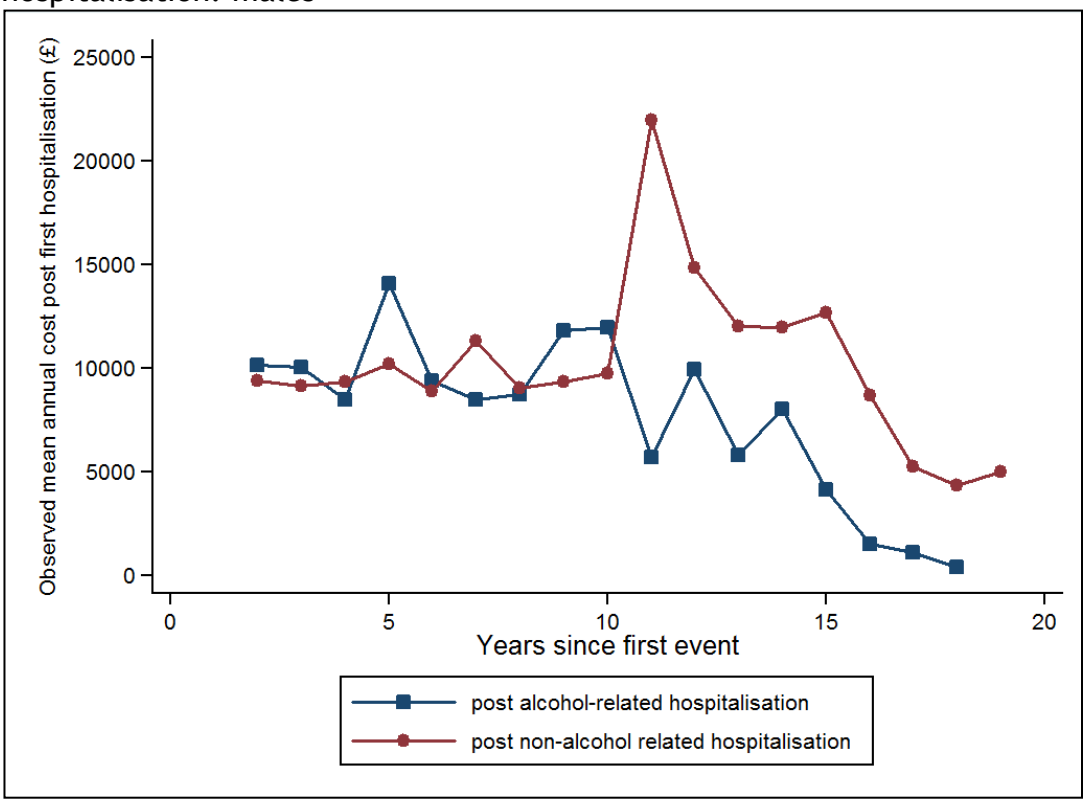


Figure 7-31 Observed mean annual hospitalisation costs post first hospitalisation: females

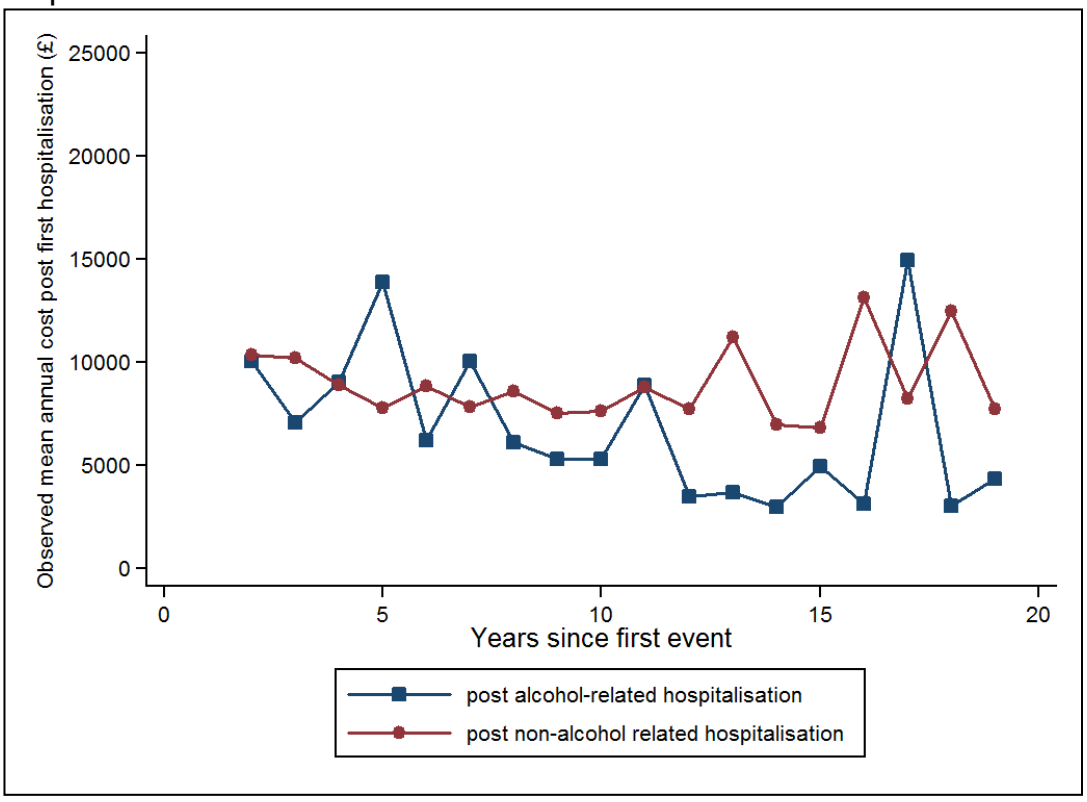


Table 7-19 Modelling annual hospitalisation costs post first hospitalisation: males

	a) post alcohol-related hospitalisation				b) post non-alcohol related hospitalisation			
Covariate*	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***
Time spline1**	0.130	-0.086	0.345	0.239	0.046	-0.029	0.120	0.229
Time spline2**	-0.494	-1.211	0.224	0.177	-0.014	-0.148	0.120	0.839
Age at first event	0.006	-0.002	0.015	0.163	0.012	0.005	0.018	<0.001
SIMD (ref.=most deprived)								
2nd	-0.149	-0.563	0.265	0.480	0.069	-0.161	0.299	0.557
3rd	-0.447	-0.808	-0.085	0.016	-0.009	-0.268	0.251	0.948
4th	-0.367	-0.680	-0.053	0.022	-0.033	-0.294	0.228	0.804
5th(least deprived)	-0.292	-0.660	0.076	0.120	0.105	-0.531	0.740	0.747
Constant	8.751	7.876	9.626	<0.001	8.274	7.782	8.765	<0.001

*Covariates were derived from generalised linear model using gamma family with log link function.

**Time spline variables are the same as shown in Table 7-6 for post alcohol-related hospitalisation model and Table 7-9 for post non-alcohol related hospitalisation model.

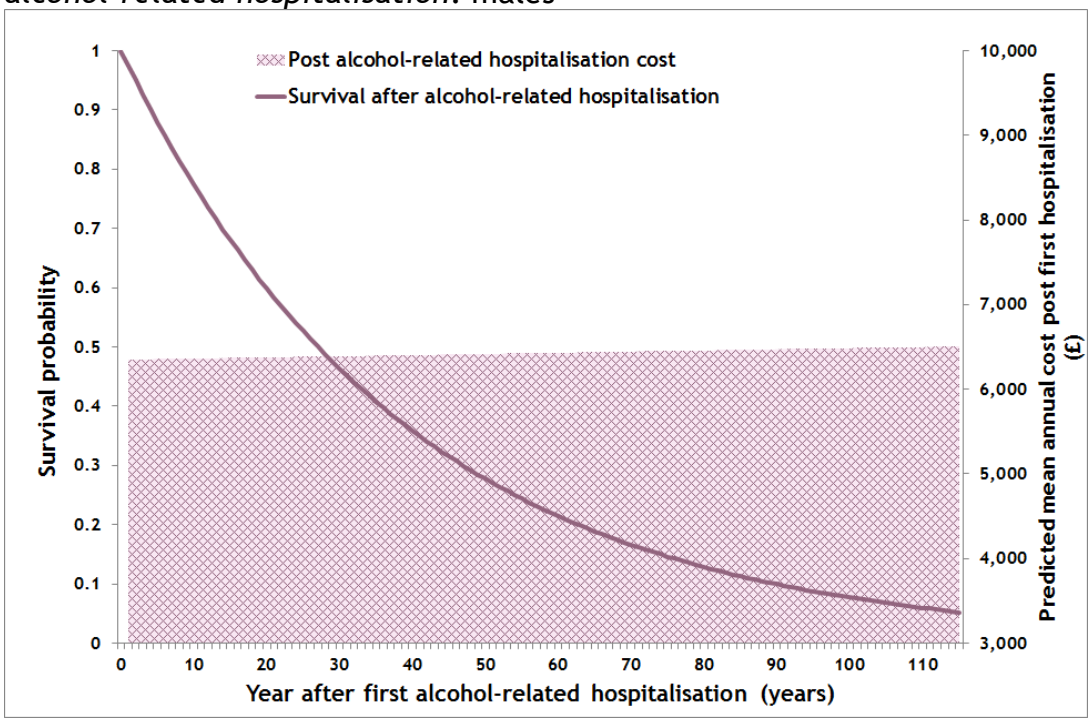
Table 7-20 Modelling annual hospitalisation costs post first hospitalisation: females

	a) post alcohol-related hospitalisation				b) post non-alcohol related hospitalisation			
Covariate*	**Coefficient**	**95%CI**		***p-value***	**Coefficient**	**95%CI**		***p-value***
Time spline1**	-0.033	-0.288	0.223	0.802	-0.103	-0.174	-0.033	0.004
Time spline2**	-0.025	-0.880	0.830	0.954	0.171	0.063	0.279	0.002
Age at first event	0.011	0.002	0.020	0.018	0.008	0.003	0.013	0.003
SIMD (ref.=most deprived)								
2nd	-0.024	-0.601	0.553	0.935	0.065	-0.179	0.308	0.601
3rd	-0.192	-0.743	0.360	0.496	-0.019	-0.219	0.182	0.856
4th	0.165	-0.461	0.792	0.605	-0.069	-0.252	0.115	0.465
5th(least deprived)	-0.177	-0.710	0.356	0.515	-0.029	-0.265	0.208	0.813
Constant	8.634	7.792	9.475	<0.001	9.016	8.531	9.501	<0.001

*Covariates were derived from generalised linear model using gamma family with log link function.

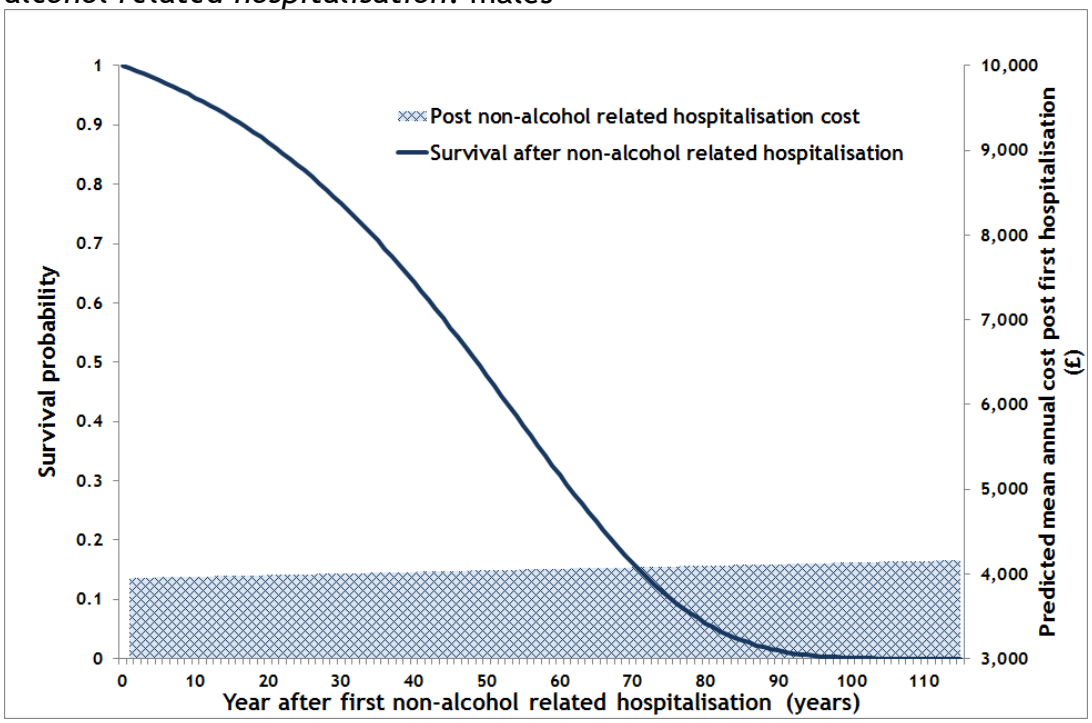
**Time spline variables are the same as shown in Table 7-6 for post alcohol-related hospitalisation model and Table 7-9 for post non-alcohol related hospitalisation model.

Figure 7-32 Predicted mean annual hospitalisation cost and survival *post alcohol-related hospitalisation*: males*



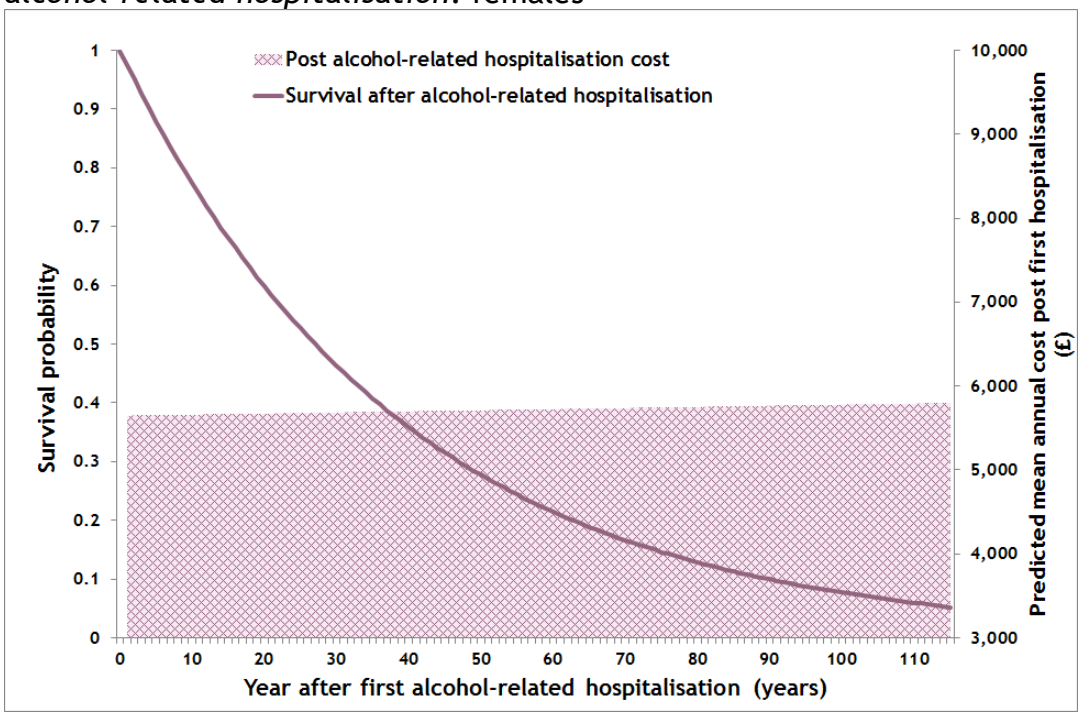
*Risk profiles: males, aged 30 years, AUDIT score=10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score. First event occurred at the same age.

Figure 7-33 Predicted mean annual hospitalisation cost and survival *post non-alcohol related hospitalisation*: males*



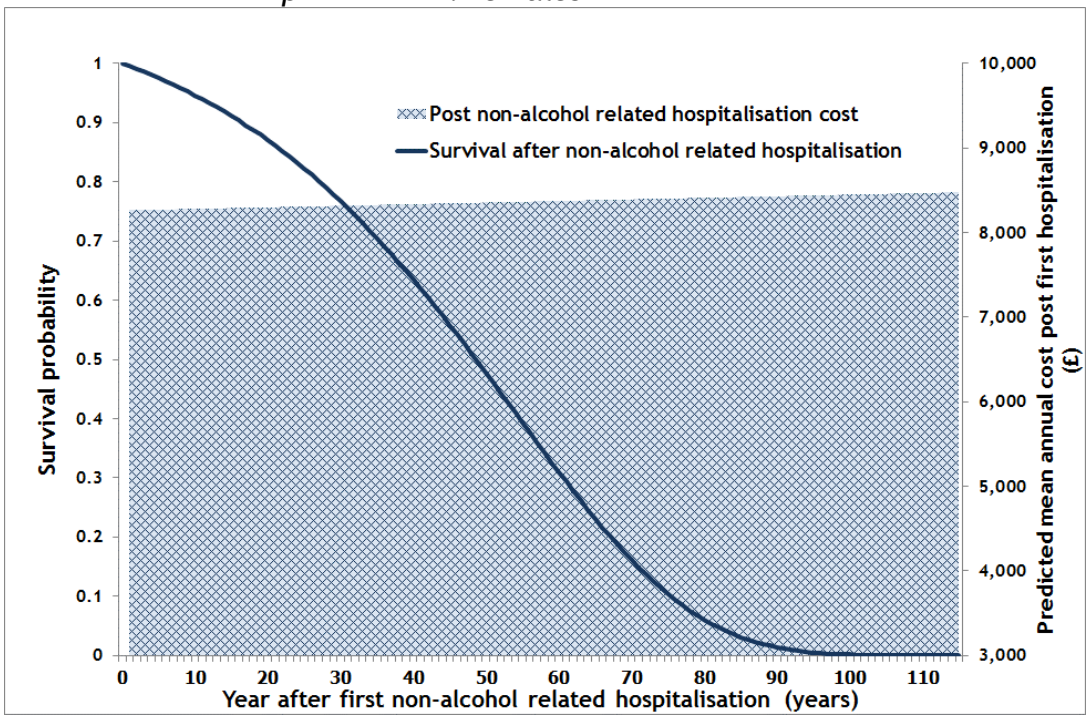
*Risk profiles: males, aged 30 years, AUDIT score=10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score. First event occurred at the same age.

Figure 7-34 Predicted mean annual hospitalisation cost and survival *post alcohol-related hospitalisation*: females*



*Risk profiles: females, aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score. First event occurred at the same age.

Figure 7-35 Predicted mean annual hospitalisation cost and survival *post non-alcohol related hospitalisation*: females*



*Risk profiles: females, aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score. First event occurred at the same age.

7.4.3 Estimated lifetime hospitalisation costs

Table 7-21 and Table 7-22 a) to c) demonstrate the three stages of predicted remaining lifetime hospitalisation costs after entering the model of individual risk profile for males and females aged 30 years, respectively. Table 7-21a and Table 7-22a represent the first stage which is the annual hospitalisation costs. It includes the costs of the first event and costs of following the first event for 100 yearly cycles. For example, if the individual risk profile of males aged 30 years had a wholly alcohol-related hospitalisation in the first year (first cycle) after the survey date, the remaining lifetime hospitalisation costs would be £279,769. Table 7-21b and Table 7-22b show the probabilities of having eight first events across 100 yearly cycles derived from the cause specific hazard model of a particular risk profile as detailed in Chapter 6. Finally, the remaining lifetime hospitalisation costs of each health state (Table 7-21a and Table 7-22a) were weighted by the probabilities of having a particular event (Table 7-21b and Table 7-22b). Subsequently, the predicted remaining lifetime hospitalisation costs after the survey date were calculated as shown in Table 7-21c and Table 7-22c. Then, the estimated remaining lifetime hospitalisation cost of defined risk profiles were £173,123 and £383,751 for males and females aged 30, respectively.

To demonstrate the use of the model for predicting lifetime hospitalisation costs, the selected factors were varied by age, group AUDIT score, smoking status and SIMD. The predicted remaining lifetime hospitalisation costs after entering model of those risk profiles are illustrated in Table 7-23 and Table 7-24 for males and females, respectively. The model shows its ability to discriminate between risk profiles as presented by different lifetime hospitalisation costs for both males and females. When other related risk profiles were changed based on the characteristic of the study population - different drinking status classified by AUDIT score - the results revealed that higher-risk drinking and more deprived status resulted in less lifetime costs.

Table 7-21 Estimating lifetime hospitalisation cost using 3 stages: males*

a) Hospitalisation cost upon entering model [Cost of first event + cost of post first event]

Cycle (years)	Wholly alcohol-related hospitalisation	Partly alcohol-related hospitalisation	Non-emergency non-CVD admission	Non-emergency CVD admission	Emergency non-CVD admission	Emergency CVD admission	Alcohol-related death	Non-alcohol related death
1	279,769	284,343	219,050	221,497	219,333	220,197	120,490	445
2	271,227	275,801	213,350	215,797	213,632	214,496	120,490	447
3	262,781	267,356	207,703	210,153	207,986	208,850	120,491	449
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
22	112,544	117,119	97,179	99,698	97,463	98,325	120,548	492
23	108,187	112,761	93,374	95,896	93,658	94,520	120,550	494
24	103,995	108,570	89,662	92,187	89,946	90,808	120,553	496
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
100	8,231	12,806	3,600	6,352	3,888	4,745	120,742	634

*Risk profiles: males, aged 30 years, AUDIT score=10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score

Table 7-21 Estimating lifetime hospitalisation cost using 3 stages: males* (cont.)

b) Probability of having eight events over yearly 100 cycles

Cycle (years)	Wholly alcohol-related hospitalisation	Partly alcohol-related hospitalisation	Non-emergency non-CVD admission	Non-emergency CVD admission	Emergency non-CVD admission	Emergency CVD admission	Alcohol-related death	Non-alcohol related death
1	0.0012	0.0037	0.0674	0.0013	0.0343	0.0022	0.0003	0.0004
2	0.0011	0.0034	0.0582	0.0012	0.0299	0.0021	0.0003	0.0004
3	0.0009	0.0032	0.0504	0.0011	0.0261	0.0019	0.0003	0.0004
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
22	0.0001	0.0012	0.0047	0.0003	0.0028	0.0008	0.0001	0.0004
23	0.0001	0.0011	0.0042	0.0003	0.0025	0.0008	0.0001	0.0004
24	0.0001	0.0011	0.0037	0.0003	0.0023	0.0008	0.0001	0.0004
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
100	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

*Risk profiles: males, aged 30 years, AUDIT score=10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score

Table 7-21 Estimating lifetime hospitalisation cost using 3 stages: males* (cont.)

c) Weighting hospitalisation cost estimated from stage a) multiplied by stage b)

Cycle (years)	Wholly alcohol-related hospitalisation	Partly alcohol-related hospitalisation	Non-emergency non-CVD admission	Non-emergency CVD admission	Emergency non-CVD admission	Emergency CVD admission	Alcohol-related death	Non-alcohol related death	***Sum***
1	343.88	1,040.71	14,763.99	280.59	7,529.23	487.83	37.82	0.17	24,484.22
2	286.79	936.91	12,420.18	250.29	6,383.12	444.23	34.94	0.17	20,756.64
3	239.67	845.17	10,471.14	223.75	5,423.22	405.42	32.36	0.17	17,640.90
.	.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.	.
22	8.86	135.26	456.36	29.93	274.01	79.94	10.82	0.19	995.38
23	7.57	124.98	391.59	27.25	236.97	74.28	10.34	0.20	873.18
24	6.48	115.52	335.95	24.81	204.90	69.01	9.88	0.20	766.76
.	.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.	.
100	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

*Risk profiles: males, aged 30 years, AUDIT score=10, binge drinking, overweight, no CVD, no diabetes, 7 cigarettes per day, medium physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score

Remaining lifetime hospitalisation cost (Cumulative sum over 100 cycles) = £173,123

Table 7-22 Estimating lifetime hospitalisation cost using 3 stages: females*

a) Hospitalisation cost upon entering model [Cost of first event + cost of post first event]

Cycle (years)	Wholly alcohol-related hospitalisation	Partly alcohol-related hospitalisation	Non-emergency non-CVD admission	Non-emergency CVD admission	Emergency non-CVD admission	Emergency CVD admission	Alcohol-related death	Non-alcohol related death
1	203,368	202,645	507,461	507,241	507,132	505,888	11,533	7,558
2	195,576	194,854	492,325	492,105	491,996	490,752	11,533	7,559
3	187,964	187,242	477,229	477,009	476,901	475,657	11,534	7,561
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
22	69,142	68,421	193,422	193,203	193,095	191,851	11,575	7,599
23	66,145	65,425	184,738	184,518	184,410	183,166	11,577	7,601
24	63,283	62,562	176,356	176,137	176,029	174,785	11,579	7,603
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
100	5,433	4,715	6,444	6,228	6,120	4,875	11,711	7,725

*Risk profiles: females, aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score

Table 7-22 Estimating lifetime hospitalisation cost using 3 stages: females* (cont.)

b) Probability of having eight events over yearly 100 cycles

Cycle (years)	Wholly alcohol-related hospitalisation	Partly alcohol-related hospitalisation	Non-emergency non-CVD admission	Non-emergency CVD admission	Emergency non-CVD admission	Emergency CVD admission	Alcohol-related death	Non-alcohol related death
1	0.0012	0.0037	0.0674	0.0013	0.0343	0.0022	0.0003	0.0004
2	0.0011	0.0034	0.0582	0.0012	0.0299	0.0021	0.0003	0.0004
3	0.0009	0.0032	0.0504	0.0011	0.0261	0.0019	0.0003	0.0004
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
22	0.0001	0.0012	0.0047	0.0003	0.0028	0.0008	0.0001	0.0004
23	0.0001	0.0011	0.0042	0.0003	0.0025	0.0008	0.0001	0.0004
24	0.0001	0.0011	0.0037	0.0003	0.0023	0.0008	0.0001	0.0004
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
100	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

*Risk profiles: females, aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score

Table 7-22 Estimating lifetime hospitalisation cost using 3 stages: females* (cont.)

c) Weighting hospitalisation cost estimated from stage a) multiplied by stage b)

Cycle (years)	Wholly alcohol-related hospitalisation	Partly alcohol-related hospitalisation	Non-emergency non-CVD admission	Non-emergency CVD admission	Emergency non-CVD admission	Emergency CVD admission	Alcohol-related death	Non-alcohol related death	***Sum***
1	178.68	1,415.18	47,807.54	403.19	20,131.60	448.90	11.75	2.96	70,399.78
2	142.60	1,191.85	38,307.17	325.93	16,313.83	389.39	11.10	2.84	56,684.69
3	114.24	1,007.61	30,805.46	264.42	13,267.74	338.98	10.53	2.73	45,811.72
.	.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.	.
22	2.41	58.82	653.54	6.63	348.46	32.36	7.04	2.46	1,111.72
23	2.02	52.03	544.45	5.57	293.57	29.18	7.02	2.49	936.33
24	1.69	46.04	453.53	4.68	247.30	26.31	7.01	2.52	789.09
.	.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.	.
100	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

*Risk profiles: females, aged 30 years, AUDIT score=6, binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, low physical activity, 3rd SIMD, prior hospitalisation over last year, and best GHQ score

Remaining lifetime hospitalisation cost (Cumulative sum over 100 cycles) = £383,751

Table 7-23 Predicted remaining lifetime hospitalisation cost classified by risks profiles: males

AUDIT score	Smoker (5 CPD)					Non-smoker				
	Age 20 years					Age 20 years				
>20	195,456	213,036	224,231	222,080	232,128	194,162	211,261	222,510	220,735	230,543
16 - 19	188,573	203,676	215,271	215,163	223,946	187,357	202,188	213,793	213,928	222,507
8 - 15	186,982	201,650	213,311	213,589	222,088	185,783	200,212	211,878	212,375	220,668
0 - 7	183,949	197,896	209,656	210,602	218,571	182,781	196,539	208,296	209,432	217,198
	Age 30 years					Age 30 years				
>20	151,956	168,646	179,675	177,982	187,919	151,120	167,397	178,499	177,106	186,854
16 - 19	147,480	161,913	173,513	173,405	182,405	146,678	160,853	172,479	172,564	181,403
8 - 15	146,429	160,453	172,152	172,341	181,136	145,633	159,426	171,144	171,518	180,147
0 - 7	144,417	157,750	169,608	170,334	178,724	143,630	156,778	168,643	169,520	177,756
	Age 40 years					Age 40 years				
>20	112,958	127,577	137,519	136,358	145,549	112,426	126,710	136,770	135,800	144,881
16 - 19	109,976	122,799	133,452	133,385	141,951	109,450	122,058	132,766	132,842	141,301
8 - 15	109,281	121,766	132,536	132,700	141,119	108,756	121,048	131,873	132,160	140,473
0 - 7	107,957	119,852	130,840	131,395	139,538	107,436	119,179	130,190	130,867	138,891
	Age 50 years					Age 50 years				
>20	80,018	91,957	100,154	99,373	107,434	79,671	91,373	99,684	99,034	107,015
16 - 19	77,864	88,499	97,492	97,407	105,064	77,529	88,002	97,060	97,075	104,664
8 - 15	77,386	87,765	96,892	96,969	104,529	77,052	87,282	96,468	96,638	104,119
0 - 7	76,494	86,413	95,793	96,142	103,520	76,164	85,956	95,380	95,812	103,111
	1	2	3	4	5	1	2	3	4	5
	most deprived				least deprived	most deprived				least deprived
	SIMD quintile									

Note: binge drinking, BMI, physical activity, CVD, diabetes, prior hospitalisation, and GHQ score were varied but not presented.

Table 7-24 Predicted remaining lifetime hospitalisation cost classified by risks profiles: females

AUDIT score	Smoker (4 CPD)					Non-smoker				
	Age 20 years					Age 20 years				
>17	434,728	483,720	491,198	494,293	527,152	433,577	482,822	490,582	492,824	526,201
13 - 16	441,952	494,935	503,292	504,088	541,190	440,249	493,250	501,815	501,971	539,332
5 - 12	444,224	498,527	507,222	507,309	545,862	442,356	496,617	505,497	504,980	543,684
0 - 4	446,176	501,601	510,627	510,112	549,931	444,158	499,494	508,682	507,625	547,525
	Age 30 years					Age 30 years				
>17	314,999	364,685	373,595	378,018	415,574	314,382	364,303	373,403	377,174	415,118
13 - 16	320,719	373,936	383,535	386,103	427,651	319,665	372,894	382,647	384,714	426,374
5 - 12	322,519	376,894	386,769	388,765	431,646	321,333	375,668	385,657	387,191	430,127
0 - 4	324,057	379,432	389,582	391,070	435,181	322,764	378,038	388,284	389,377	433,419
	Age 40 years					Age 40 years				
>17	213,804	255,168	263,415	267,836	302,142	213,601	255,230	263,587	267,547	302,159
13 - 16	218,111	262,350	271,075	274,136	311,930	217,604	261,921	270,716	273,421	311,275
5 - 12	219,050	264,650	273,577	276,174	315,175	218,864	264,059	273,043	275,345	314,301
0 - 4	220,639	266,630	275,767	277,991	318,048	219,933	265,905	275,068	277,035	316,986
	Age 50 years					Age 50 years				
>17	137,475	168,171	174,801	178,414	205,394	137,563	168,500	175,184	178,520	205,760
13 - 16	140,531	173,419	180,362	183,006	212,857	140,370	173,379	180,351	182,801	212,703
5 - 12	141,496	175,100	182,186	184,492	215,349	141,267	174,944	182,050	184,210	215,005
0 - 4	142,312	176,534	183,780	185,835	217,575	142,026	176,301	183,536	185,452	217,083
	1	2	3	4	5	1	2	3	4	5
	most deprived				least deprived	most deprived				least deprived
	SIMD quintile									

Note: binge drinking, BMI, physical activity, CVD, diabetes, prior hospitalisation, and GHQ score were varied but not presented.

7.5 Discussion

This study used the alcohol intervention model which was developed from the analyses of SHeS-SMR linked datasets combined with the health state transition model to estimate long-term consequences, i.e. life expectancy (as shown in Chapter 6), QALYs, and lifetime hospitalisation costs as presented in this chapter. Lifetime QALYs and costs are widely recommended for the purpose of economic evaluation informing policy decision-making regarding healthcare intervention (ISPOR, 2014, NICE, 2013, Chaikledkaew and Kittrongsiri, 2014, Teerawattananon and Chaikledkaew, 2008); these standard methods are also applied for public health intervention (Edwards et al., 2013, Weatherly et al., 2009). Key components that were also modelled to calculate QALYs are shown as follows: 1) estimating baseline HRQoL score by gender and SIMD (as detailed in Chapter 5); 2) modelling utility decrement due to hospitalisation and increasing AUDIT score (as detailed in Chapter 5); 3) modelling risks of having six subsequent hospitalisations after first events via separated models classified by gender and first hospitalisation condition (i.e. alcohol-related and non-alcohol related conditions) - which assessed internal validity by comparing to the observed data; and 4) modelling survival following the first hospitalisation conditions (as described in Chapter 6). Eventually, the predicted remaining QALYs after entering the model were derived from those components.

For estimating lifetime hospitalisation costs, the main inputs were: 1) Scottish health services costs ('Cost book'), which detailed the cost per bed day of the specific specialty and health board; 2) modelling annual hospitalisation costs in the year of having the first event; and 3) annual hospitalisation costs in following years after the first event. Then, the lifetime hospitalisation costs after entering the model were estimated using the average yearly hospitalisation costs adjusted by predicted survival, the same method as estimating QALY. Moreover, the estimated costs and QALYs were presented via different selected risk profiles classified by age, gender, socioeconomic status, and selected risk behaviours. Drinking status, one of the selected risk behaviours, varied from low-risk to high-risk drinking depending on the AUDIT

score. These results can demonstrate the use of model to estimate and compare lifetime QALYs and healthcare costs across drinking patterns and other relevant risk profiles. The results of this study indicate how the consequences on health and healthcare cost can change in the long-term, attributable to either an increase or decrease alcohol consumption (measured by the AUDIT). When comparing different drinking statuses classified by the AUDIT score, higher-risk drinking (higher score) was found to have resulted in lower remaining predicted QALYs and predicted lifetime costs than low-risk drinking for both males and females.

The use of a modelling approach for the evaluation of alcohol policies and interventions has been increasingly applied for informing policy decision-makers (Ashley et al., 2015, Barbosa et al., 2015, Barbosa et al., 2010b, Brennan et al., 2014a, Brennan et al., 2014b, Cadilhac et al., 2011, Chisholm et al., 2004, Galea et al., 2009, Holmes et al., 2014a, Marsh et al., 2012, Byrnes et al., 2010, Cobiac et al., 2009, Purshouse et al., 2013). Nevertheless, the findings of the current study could not be compared to the findings of previous studies because of the various issues surrounding the methodology as described in Chapter 6. In addition, the current alcohol intervention model analysed Scottish longitudinal data (SHeS-SMR linkage data) to estimate HRQoL, QALYs, and healthcare costs so it can be seen that these estimations were based on a Scottish-specific setting. As generally suggested by economic evaluation guidelines, those outcomes and costs should be setting-specific, and hence are not transferable across jurisdictions (Barbieri et al., 2010, Drummond et al., 2015, Drummond et al., 2009, Goeree et al., 2007, Goeree et al., 2011). Even though this study estimated healthcare costs and QALYs similar to Barbosa et al. (Barbosa et al., 2015, Barbosa et al., 2010b) - which modelled long-term costs and outcomes from multiple sources of input parameters - this study analysed single longitudinal linkage data. The results of this study could be specifically applied to the Scottish context with good internal validity (as presented in Chapter 6), whereas the results may be lack external validity.

However, the use of model calibration can be applied to make this model more transferable to other settings.

Some important limitations need to be considered for estimating QALYs and lifetime hospitalisation costs. First, this study constructed a model of health-related harms to the individual drinker, i.e. morbidity and mortality, whereas wider harms were discussed in the literature and recommended for inclusion in the evaluation of public health interventions (e.g. effects on family members and workplace, risks of social harms, and loss of work productivity) (Edwards et al., 2013, Weatherly et al., 2009). However, these harms were excluded due to limited resources for primary research within this study. Thus, the lifetime consequences of drinking at a high-risk level would be underestimated. Further studies should take into account the societal perspective of both costs and outcomes combined with the long-term consequences of individual drinkers to capture a wider range of alcohol-related harms. Second, there were no longitudinal data related to drinking status (measured by the predicted AUDIT). As HRQoL changes over time, the analyses of long-term consequences assumed that the AUDIT score of the study cohort were unchanged from the baseline at survey date. However, age-related HRQoL might be varied over time.

Third, the reduction of HRQoL due to hospitalisation was estimated from past admission under the assumption that it affected current health status of the study population. Due to the lack of longitudinal HRQoL data after the survey date, the analysis applied these values to estimate the effects of further hospitalisations on utility decrement, as well as to estimate lifetime QALYs. Fourth, the hospitalisation conditions in this analysis were classified by alcohol attribute and emergency admission with or without CVD of primary diagnosis. As such, the different severity of diseases related to HRQoL and LOS of each hospitalisation episode (used for estimating healthcare costs) were combined in each classification. However, the magnitude of any estimation bias is difficult to define. Finally, this study used per diem costing and employed the Scottish

'Cost book' at the specialty level classified by each NHS regional health board since there were no Scottish data at the healthcare groups (HRG)-level (Information Services Division (ISD), 2013). HRG-level data would have been able to define the use of healthcare resources for clinically similar treatments commonly used for healthcare cost estimation. The approach used in this study explained that derived costs were higher than using HRG estimation (Geue et al., 2012). Thus, the lifetime healthcare costs might not represent the actual healthcare costs of the Scottish population. However, these costs would be useful for comparison across risk profiles of the study population.

7.6 Conclusions

Lifetime QALYs and costs are generally recommended for the purposes of economic evaluation of healthcare interventions to inform policy decision-making. This chapter illustrated the use of a current alcohol intervention model to estimate the economic evaluation outcome, i.e. QALYs and costs over lifetime, generating these outcomes for different risk profiles. The results also presented the estimated QALYs and healthcare costs of alcohol consumption at various levels of risk so the application of the model can be used for the economic evaluation of alcohol interventions which aim to modify drinking pattern (as measured by the AUDIT) among various target groups (e.g. age, gender, and socioeconomic status). The full economic evaluation will be described in the next chapter.

Chapter 8: The use of an alcohol intervention model for economic evaluation

8.1 Introduction

This chapter demonstrates an economic evaluation of a hypothetical alcohol intervention for high-risk alcohol drinking assessed by the AUDIT by using the alcohol intervention model developed in earlier chapters. Moreover, the model will be used to predict lifetime healthcare cost and outcomes (i.e. LYs and QALYs) related to other selected risk behaviours (e.g. cigarette per day) which were included in the model as covariates (as described in Chapters 6 and 7). Thus, the developed model to determine cost-effectiveness can be used to perform not only an alcohol intervention evaluation but it can also be combined with other modified risk behaviours intervention, e.g. increased cigarette tax and anti-smoking legislation, which were found to be associated with reductions in alcohol consumption among populations in the U.S. and Italy, respectively (Young-Wolff et al., 2014, Pieroni et al., 2013). Moreover, modified multiple unhealthy behavioural changes was suggested by previous RCTs to be more effective than single targeted behaviour changes (Prochaska et al., 2012, Kruger et al., 2014, Schulz et al., 2014).

This analysis illustrates the model-based economic evaluation of the hypothetical intervention which aims to change alcohol drinking and smoking. The purpose of the analysis is to supplement a within-trial cost-effectiveness analysis using a modelling approach to estimate long-term cost-effectiveness. This chapter details the framework of conducting the economic evaluation as follows: 1) study design and analytical model structure; 2) required input parameters and uncertainty analysis of input parameters; and 3) discounting future cost and outcome. Furthermore, cost-effectiveness results will be presented using a probabilistic model which takes into account parameter uncertainty; the results will then be compared to a cost-effective threshold based on the UK advisory body's judgement of £20,000 per QALY gained for

which interventions are considered to be cost-effective (National Institute for Health and Care Excellence (NICE), 2012).

8.2 Methods

8.2.1 Study design

To conduct an economic evaluation comparing the costs and benefits of new interventions with the control group, a within-trial analysis is used to estimate the short-term cost-effectiveness of interventions while longer-term cost-effectiveness is assessed by an economic model to estimate lifetime costs and benefits of the compared interventions. This study developed an alcohol intervention model which will be used to estimate the long-term cost-effectiveness of an intervention that aims to change selected risk factors. The model was designed to convert changes in risk factors into long-term LYs, QALYs, and lifetime healthcare costs, and its structure is illustrated in Figure 8-1. The selected risk factors i.e. alcohol drinking (the AUDIT, and binge drinking), number of cigarettes per day, physical activity, and BMI will be measured during the within-trial follow-up period, and this session assumes that a hypothetical intervention will result in study cohorts quitting their drinking and smoking behaviours. A within-trial cost-effectiveness analysis (short-term) will be performed using cost analysis and the outcome measurement (i.e. HRQoL) within the follow-up period. Then, the health state transition model (Figure 8-1) will be used to conduct a long-term cost-effectiveness analysis to predict the lifetime cost, LYs, and QALYs due to changes in risk behaviours in the follow-up period when comparing between the intervention and control groups.

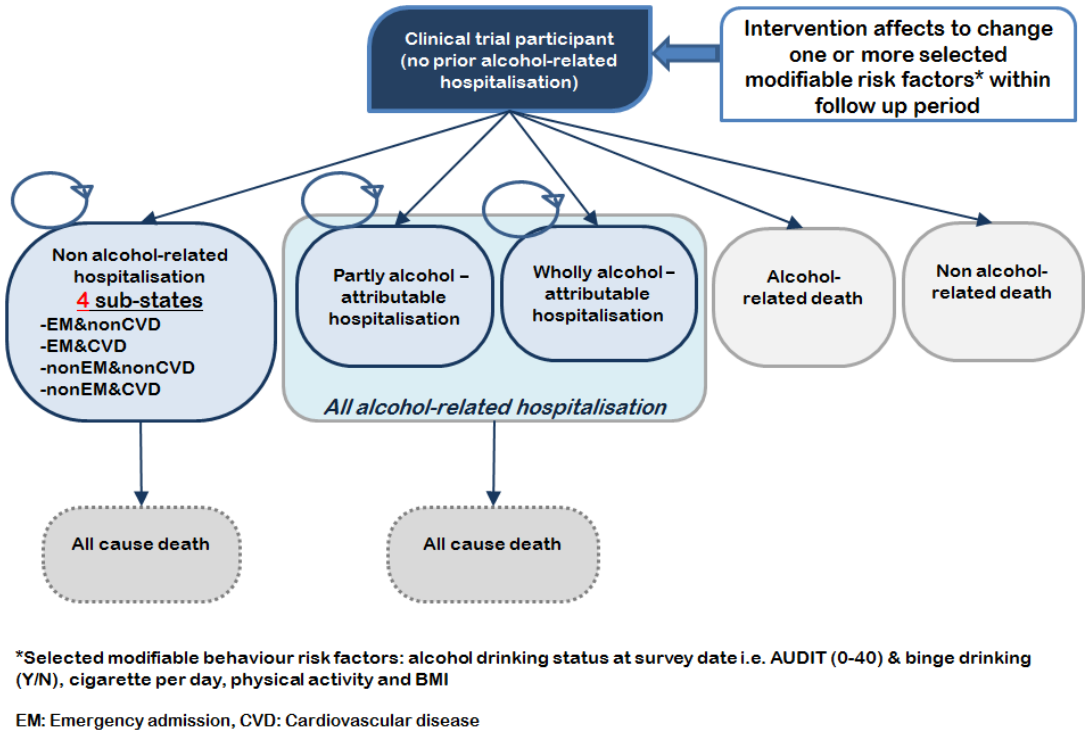


Figure 8-1 Structure of the health state transition model and intervention effect for economic evaluation

Cost-utility analysis (CUA)

To estimate the cost-effectiveness of an intervention that aims to modify selected risk factors, two scenarios of the model are performed for each individual risk profile. The first scenario estimates lifetime costs and health outcomes (i.e. LYs and QALYs) of baseline risk profiles where the functions of risk profiles were presented in Chapter 6: and the function of costs and HRQoL were described in Chapter 7:. The second scenario estimates the costs and outcomes of changes in risk behaviours (e.g. quitting smoking and drinking) brought about by the intervention's effects on these modifiable risk factors, leading to changes of first hospitalisation and death risks (as described in Chapter 6:) as well as healthcare costs and QALY (as described in Chapter 7:). Next, the estimated lifetime hospitalisation costs and health outcomes are compared between the baseline and intervention scenarios. Incremental-cost effectiveness ratio (ICER) - the additional cost per additional unit of effect (i.e. QALY) from a new intervention – is also computed as the ICER of CUA is the

incremental cost per QALY gained (Briggs et al., 2006c, Drummond MF et al., 1997, Gray et al., 2011a). Then, the ICER of the intervention will be compared to the threshold ICER based on the UK advisory body's judgement that interventions with an ICER of less than £20,000 per QALY gained are considered to be cost effective (National Institute for Health and Care Excellence (NICE), 2012).

8.2.2 Input parameters

This stage describes the input parameters required for an economic evaluation using the developed model to predict LYs, QALYs, and lifetime costs. This model can be used for generating a hypothetical intervention and determining its cost-effectiveness. To demonstrate how the model works, this analysis assumed that a hypothetical intervention aimed at stopping smoking and hazardous alcohol drinking (AUDIT score of 8-15 for males and 5-12 for females) in different aged groups and gender had a combined cost of £60 per person per year. This analysis performed the estimated costs and health outcomes of two scenarios as mentioned above. For the control group, the base-case scenario estimated the lifetime consequences of different baseline risk profiles of the SHeS population; this was done during the development of alcohol intervention model. For the second intervention scenario, the effects of the intervention on modifying risk behaviours (i.e. stopping smoking and drinking) resulted in the changes of morbidity and mortality risks from the baseline, leading to differences in estimated lifetime costs and health outcomes compared to the base-case.

Intervention effectiveness

To apply one of the recommended frameworks for evaluating the public health impact of health promotion interventions (Glasgow et al., 1999) - namely the RE-AIM framework - intervention effectiveness should be assessed via five dimensions as follows:

1) ***R****each*: proportion of the target population that participated in the intervention

2) ***E****fficacy*: success rate if implemented as recommended in the guidelines, defined as positive outcomes minus negative outcomes
3) ***A****doption*: proportion of settings, practices, and plans that will adopt the intervention
4) ***I****mplementation*: extent to which the intervention is implemented as intended in the real world
5) ***M****aintenance*: extent to which the intervention is sustained overtime

These dimensions can be evaluated at multiple levels, e.g. individual, healthcare setting, community or population.

To analyse the cost-effectiveness of a health promotion intervention, the intervention effectiveness should take these dimensions in the model into account. Firstly, the coverage rate and acceptance rate of the intervention should be defined to estimate the proportion of the target population and the proportion of setting that would adopt the intervention (Glasgow et al., 1999). Secondly, the efficacy of intervention on modifying selected risk behaviours (as shown in Figure 8-1) within the follow-up period should be collected from individual who participated in an RCT or as an evidence synthesis of RCTs and observational studies, where the target population should be clearly described and relevant to the population of the intervention under evaluation. Thirdly, since the effect of a health promotion intervention may change over time (Green and Tones, 1999), the lag time of partial and full effects of the intervention should be defined and take into account in the effectiveness of the modelled intervention. Moreover, the lag time of these effects should be captured either within-trial (short-term period), e.g. change of risk behaviours, or in a longer-term period, e.g. changes of morbidity and mortality (Holmes et al., 2012). Finally, to examine the long-term maintenance of behaviour change due to the intervention, the duration of the intervention's effects should be considered as well as the extent to which the intervention is implemented in a real-world situation (Glasgow et al., 1999). For the hypothetical intervention in this analysis, it was assumed that the intervention resulted in participants quitting their drinking and smoking behaviours in the first year of implementation. Subsequently, all the participants would then receive this

intervention every year to maintain the same risk behaviours as in the first year. To simplify the demonstration of the model, a coverage rate and acceptance rate of 100% were applied.

Intervention costs

This analysis was conducted from an NHS perspective so direct medical costs and intervention costs incurred on provider's side were included. To analyse short-term cost-effectiveness, the intervention costs were collected within-trial which consisted of the cost of development and implementation in an RCT setting, and the cost of full implementation to other settings were estimated to reflect the real-world situation of the adopted intervention (Kruger et al., 2014). To demonstrate the use of model, this analysis assumed the intervention costs were £60 per year. For the longer-term cost-effectiveness analysis, the lifetime hospitalisation costs were estimated with the same approach as the base-case (as described in Chapter 7); it should be noted that the healthcare costs of the intervention were affected by the intervention's effectiveness, leading to a change in the risk of hospitalisation. Both short-term costs and long-term costs were then combined to achieve the estimated total costs of the intervention.

8.2.3 Discounting

As recommended by NICE, a discount rate of 1.5% for all costs and benefits was used since public health interventions usually show their effect over the long-term (National Institute for Health and Care Excellence (NICE), 2012). Thus, this analysis employed a discounting rate of 1.5% for all future costs and QALYs.

8.2.4 Uncertainty analysis

A probabilistic sensitivity analysis (PSA) was conducted to assess the uncertainty surrounding the input parameters of the model (Appendix 8) that were mostly derived from multivariate regression analyses, where these parameters were known their covariance relationship in the regression

frameworks (Briggs, 2000). Thus, the uncertainty analysis was performed using a variance-covariance matrix of these parameters to show the covariance relationship, and the Cholesky decomposition was employed to generate correlated random parameters from the multivariate standard normal distribution as presented in Appendix 9 (Briggs et al., 2006a). The next stage, a Monte Carlo simulation performed in Microsoft Excel 2010 (Microsoft Corp., Redmond, WA) was employed to generate 5,000 iterations to demonstrate a range of plausible lifetime costs, health outcomes (LYs and QALYs), and ICERs (Appendix 9).

The result of the analysis was plotted in a cost-effectiveness plane (Briggs et al., 2006b, Black, 1990) which shows the difference (intervention minus base case) in effectiveness (△E) per patient on the horizontal axis versus the difference in cost (△C) per patient on the vertical axis. The slope of the graph was computed using the equation ICER =△C/△E. When the ICER simulations were compared to the cost-effectiveness (CE) threshold of £20,000/QALY gained, the simulations which had a lower slope than the threshold line were considered to be cost-effective. Moreover, to summarise uncertainty by considering how many of the ICER simulations on the cost-effectiveness plane fall below and to the right of different thresholds, a cost-effectiveness acceptability curve (CEAC) was used to illustrate this uncertainty (van Hout et al., 1994, Briggs et al., 2006b, Fenwick et al., 2001, Briggs, 2000). The results were then further analysed for to determine a relationship between the different values of the threshold and the likelihood of being a cost-effective option compared between the base-case and hypothetical intervention using a net monetary benefit framework. The net monetary benefit (NMB) employs the cost-effectiveness decision rule (ICER< ceiling threshold referred as λ) by rearranging the equation as follows:

$$\frac{\Delta C}{\Delta E} < \lambda$$

$$\Delta E \times \lambda - \Delta C > 0$$

The intervention is considered cost-effective if its NMB is positive at any value of the ceiling threshold. Using the results of the Monte Carlo simulation (5,000 iterations), the NMB of each iteration of the intervention was calculated

and compared to the base-case at the specific threshold, and the proportion of these cost-effective iterations (NMB>0) were then plotted CEAC.

8.3 Demonstrating results

8.3.1 Cost-utility analysis

Table 8-1 to Table 8-6 demonstrate the results derived from probabilistic model, where the uncertainty of input parameters was accounted for using Monte Carlo simulations. The results present the average and 95% credible interval of undiscounted LYs, remaining discounted QALYs and remaining discounted costs compared between the base-case and hypothetical intervention - where it was assumed that the intervention's effect would result in the quitting of smoking and drinking among study cohorts, and the intervention would cost £60 per person per year. The "best-case" scenario was demonstrated based on the existing alcohol interventions in Thailand which the developed model will be adapted. The first importance intervention is a campaign known as "No alcohol during Buddhist Lent" which has been launched to encourage people to refrain from drinking alcoholic beverage during the three-month period of Buddhist Lent in every year since 2003 (SAB and (Research Centre for Social and Business Development Co., 2016). Moreover, two national surveys reported concurrent cigarette smoking and alcohol consumption, so the combined interventions between control alcohol drinking and smoking have been increasingly interested by Thai stakeholders as well as screening and concurrent brief intervention of conjoint hazardous or harmful alcohol and tobacco use in hospital is developing (Aekplakorn et al., 2008, Intarut and Pukdeesamai, 2017, Pengpid et al., 2015).

For the comparison of LYs between the base-case and the intervention (as shown in Table 8-1 for males and Table 8-2 for females), the average LYs of the interventions for those who stopped smoking and alcohol drinking showed a longer life expectancy than the base-case across all age groups and risk profiles. Life expectancies of the intervention group ranged from 74.05 to 85.90 years for males and 72.45 to 88.47 years for females, whereas life expectancies

of the base-case ranged from 72.09 to 85.79 years for males and 71.24 to 88.28 years for females.

Table 8-3 and Table 8-4 present the remaining discounted QALYs from age at the start of input into the model and varied by risk profiles for males and females, respectively. These average QALYs can be used for future cost-effectiveness analyses that compare the difference of discounted QALYs (△E) and discounted costs (△C) between the base-case and intervention since the beginning of the model's cohort, so QALYs and costs prior starting cohort are not included for estimating ICERs (△C/△E). When comparing the base-case to the intervention in terms of estimated remaining discounted QALYs, it was revealed that the intervention had higher discounted QALYs than the base-case across all age groups, drinking patterns, and smoking status. The additional QALYs (years) obtained from quitting drinking and smoking ranged from 0.07 to 0.90 for males and 0.06-0.97 for females.

The remaining discounted costs based on the provider perspective of the base-case (including healthcare costs) and the intervention (i.e. intervention cost and healthcare costs) are illustrated in Table 8-5 for males and Table 8-6 females in the same fashion as how QALYs were earlier presented. For males, the intervention resulted in less costs than the base-case for all drinking and smoking patterns in study cohorts aged 20 and 30 years. In this case, the intervention – which aimed to stop drinking and smoking for these groups - dominates the base-case due to more cost-savings in the long run as well as more QALYs as mentioned above. For older males aged 40 and 50 years as well as females of all ages, the results showed variation of incremental costs across risk profiles which varied from intervention being cost-saving to higher cost than base-case.

Table 8-1 Predicted life expectancy compared between the base-case and intervention classified by risks profiles: males

Age (years)	**20**				**30**			
Base case modifiable risk factors								
Drinking status	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence
AUDIT score	0 - 7	8 - 15	16 - 19	>20	0 - 7	8 - 15	16 - 19	>20
Predicted life expectancy (years): base case	**85.78**	**80.06**	**79.79**	**79.06**	**83.04**	**77.72**	**77.63**	**72.87**
95% credible interval	(85.63,85.93)	(79.92,80.19)	(79.66,79.93)	(78.92,79.2)	(82.92,83.17)	(77.62,77.82)	(77.53,77.73)	(72.78,72.97)
Predicted life expectancy (years): intervention*	**85.90**	**80.92**	**80.76**	**80.83**	**83.19**	**78.35**	**78.40**	**75.25**
95% credible interval	(85.74,86.05)	(80.78,81.05)	(80.63,80.9)	(80.69,80.96)	(83.07,83.31)	(78.25,78.45)	(78.3,78.5)	(75.16,75.34)

*The results of intervention demonstrate that the intervention result in the stoppage of drinking and smoking for all groups.
Note: The results were derived from a probabilistic model using 5,000 simulations. BMI, SIMD, CVD, diabetes, prior hospitalisation, and GHQ score were varied for baseline risk profiles but not presented.

Table 8-1 Predicted life expectancy compared between the base-case and the intervention classified by risks profiles: males (cont.)

Age (years)	**40**				**50**			
Base case modifiable risk factors								
Drinking status	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence
AUDIT score	0 - 7	8 - 15	16 - 19	>20	0 - 7	8 - 15	16 - 19	>20
Predicted life expectancy (years): base case	**80.62**	**80.43**	**73.13**	**72.09**	**77.44**	**77.08**	**76.89**	**76.04**
95% credible interval	(80.54,80.7)	(80.35,80.51)	(73.08,73.19)	(72.03,72.15)	(77.39,77.49)	(77.04,77.13)	(76.85,76.94)	(75.99,76.09)
Predicted life expectancy (years): intervention*	**80.98**	**81.03**	**74.05**	**74.08**	**77.64**	**77.60**	**77.61**	**77.62**
95% credible interval	(80.89,81.06)	(80.95,81.11)	(73.99,74.11)	(74.02,74.13)	(77.6,77.69)	(77.55,77.64)	(77.57,77.66)	(77.57,77.66)

*The results of intervention demonstrate that the intervention would result in the stoppage of drinking and smoking for all groups.
Note: The results were derived from a probabilistic model using 5,000 simulations. BMI, SIMD, CVD, diabetes, prior hospitalisation, and GHQ score were varied for baseline risk profiles but not presented.

Table 8-2 Predicted life expectancy compared between the base-case and the intervention classified by risks profiles: females

Age (years)	**20**				**30**			
Base case modifiable risk factors								
Drinking status	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence
AUDIT score	0-4	5-12	13-16	>17	0-4	5-12	13-16	>17
Predicted life expectancy (years): base case	**88.28**	**87.52**	**80.20**	**79.24**	**85.24**	**75.52**	**75.18**	**74.30**
95% credible interval	(88.1,88.46)	(87.34,87.69)	(80.03,80.37)	(79.07,79.42)	(85.08,85.4)	(75.39,75.64)	(75.06,75.31)	(74.17,74.42)
Predicted life expectancy (years): intervention*	**88.47**	**88.46**	**81.02**	**81.08**	**85.45**	**75.92**	**75.79**	**75.78**
95% credible interval	(80.86,81.08)	(80.81,81.04)	(80.91,81.13)	(72.38,72.53)	(75.33,75.43)	(74.84,74.95)	(74.25,74.36)	(74.22,74.32)

*The results of intervention demonstrate that the intervention would result in the stoppage of drinking and smoking for all groups.
Note: The results were derived from a probabilistic model using 5,000 simulations. BMI, SIMD, CVD, diabetes, prior hospitalisation, and GHQ score were varied for baseline risk profiles but not presented.

Table 8-2 Predicted life expectancy compared between the base-case and the intervention classified by risks profiles: females (cont.)

Age (years)	**40**				**50**			
Base case modifiable risk factors								
Drinking status	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence
AUDIT score	0-4	5-12	13-16	>17	0-4	5-12	13-16	>17
Predicted life expectancy (years): base case	**80.77**	**80.54**	**80.41**	**71.24**	**75.20**	**74.67**	**73.82**	**72.20**
95% credible interval	(88.1,88.46)	(87.34,87.69)	(80.03,80.37)	(79.07,79.42)	(85.08,85.4)	(75.39,75.64)	(75.06,75.31)	(74.17,74.42)
Predicted life expectancy (years): intervention*	**80.97**	**80.93**	**81.02**	**72.45**	**75.38**	**74.90**	**74.31**	**74.27**
95% credible interval	(80.86,81.08)	(80.81,81.04)	(80.91,81.13)	(72.38,72.53)	(75.33,75.43)	(74.84,74.95)	(74.25,74.36)	(74.22,74.32)

*The results of intervention demonstrate that the intervention would result in the stoppage of drinking and smoking for all groups.
Note: The results were derived from a probabilistic model using 5,000 simulations. BMI, SIMD, CVD, diabetes, prior hospitalisation, and GHQ score were varied for baseline risk profiles but not presented.

Table 8-3 Predicted remaining discounted QALY compared between the base-case and the intervention classified by risks profiles: males

Age (years)	**20**				**30**			
Base case modifiable risk factors								
Drinking status	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence
AUDIT score	0 - 7	8 - 15	16 - 19	>20	0 - 7	8 - 15	16 - 19	>20
Predicted remaining discounted QALY (years) : base case	**32.02**	**27.91**	**27.24**	**24.46**	**27.48**	**23.47**	**22.91**	**18.15**
95% credible interval	(31.97,32.06)	(27.87,27.95)	(27.2,27.28)	(24.41,24.51)	(27.44,27.52)	(23.44,23.51)	(22.87,22.94)	(18.11,18.19)
Predicted remaining discounted QALY (years) : intervention*	**32.09**	**28.26**	**27.65**	**25.18**	**27.56**	**23.76**	**23.26**	**19.05**
95% credible interval	(32.05,32.13)	(28.22,28.3)	(27.6,27.69)	(25.13,25.23)	(27.53,27.6)	(23.72,23.79)	(23.22,23.29)	(19.02,19.09)

*The results of intervention demonstrate that the intervention would result in the stoppage of drinking and smoking for all groups.
Note: The results were derived from a probabilistic model using 5,000 simulations. BMI, SIMD, CVD, diabetes, prior hospitalisation, and GHQ score were varied for baseline risk profiles but not presented.

Table 8-3 Predicted remaining discounted QALY compared between the base-case and the intervention classified by risks profiles: males (cont.)

Age (years)	**40**				**50**			
Base case modifiable risk factors								
Drinking status	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence
AUDIT score	0 - 7	8 - 15	16 - 19	>20	0 - 7	8 - 15	16 - 19	>20
Predicted remaining discounted QALY (years) : base case	**22.51**	**21.49**	**16.36**	**14.35**	**16.33**	**15.47**	**15.02**	**13.25**
95% credible interval	(22.48,22.54)	(21.46,21.52)	(16.34,16.38)	(14.32,14.38)	(16.3,16.35)	(15.45,15.49)	(14.99,15.04)	(13.23,13.28)
Predicted remaining discounted QALY (years) : intervention*	**22.67**	**21.77**	**16.77**	**15.16**	**16.45**	**15.75**	**15.41**	**14.04**
95% credible interval	(22.64,22.7)	(21.74,21.8)	(16.75,16.79)	(15.13,15.19)	(16.43,16.47)	(15.73,15.77)	(15.39,15.43)	(14.01,14.06)

*The results of intervention demonstrate that the intervention would result in the stoppage of drinking and smoking for all groups.
Note: The results were derived from a probabilistic model using 5,000 simulations. BMI, SIMD, CVD, diabetes, prior hospitalisation, and GHQ score were varied for baseline risk profiles but not presented.

Table 8-4 Predicted remaining discounted QALY compared between the base-case and the intervention classified by risks profiles: females

Age (years)	**20**				**30**			
Base case modifiable risk factors								
Drinking status	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence
AUDIT score	0-4	5-12	13-16	>17	0-4	5-12	13-16	>17
Predicted remaining discounted QALY (years) : base case	**29.46**	**28.46**	**25.21**	**23.54**	**26.84**	**20.68**	**20.27**	**18.92**
95% credible interval	(29.42,29.51)	(28.41,28.5)	(25.17,25.25)	(23.48,23.59)	(26.8,26.89)	(20.64,20.71)	(20.24,20.31)	(18.88,18.96)
Predicted remaining discounted QALY (years) : intervention*	**29.56**	**28.77**	**25.47**	**24.22**	**26.96**	**20.81**	**20.49**	**19.46**
95% credible interval	(21.65,21.72)	(21.09,21.16)	(20.83,20.9)	(14.84,14.91)	(15.05,15.09)	(14.3,14.34)	(13.36,13.41)	(12.67,12.72)

*The results of intervention demonstrate that the intervention would result in the stoppage of drinking and smoking for all groups.
Note: The results were derived from a probabilistic model using 5,000 simulations. BMI, SIMD, CVD, diabetes, prior hospitalisation, and GHQ score were varied for baseline risk profiles but not presented.

Table 8-4 Predicted remaining discounted QALY compared between the base-case and the intervention classified by risks profiles: females (cont.)

Age (years)	**40**				**50**			
Base case modifiable risk factors								
Drinking status	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence
AUDIT score	0-4	5-12	13-16	>17	0-4	5-12	13-16	>17
Predicted remaining discounted QALY (years) : base case	**21.57**	**20.99**	**20.62**	**14.39**	**14.97**	**14.26**	**13.19**	**11.72**
95% credible interval	(29.42,29.51)	(28.41,28.5)	(25.17,25.25)	(23.48,23.59)	(26.8,26.89)	(20.64,20.71)	(20.24,20.31)	(18.88,18.96)
Predicted remaining discounted QALY (years) : intervention*	**21.68**	**21.12**	**20.86**	**14.87**	**15.07**	**14.32**	**13.39**	**12.69**
95% credible interval	(21.65,21.72)	(21.09,21.16)	(20.83,20.9)	(14.84,14.91)	(15.05,15.09)	(14.3,14.34)	(13.36,13.41)	(12.67,12.72)

*The results of intervention demonstrate that the intervention would result in the stoppage of drinking and smoking for all groups.
Note: The results were derived from a probabilistic model using 5,000 simulations. BMI, SIMD, CVD, diabetes, prior hospitalisation, and GHQ score were varied for baseline risk profiles but not presented.

Table 8-5 Predicted remaining lifetime hospitalisation discounted cost compared between the base-case and the intervention classified by risks profiles: males

Age (years)	**20**				**30**			
Base case modifiable risk factors								
Drinking status	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence
AUDIT score	0 - 7	8 - 15	16 - 19	>20	0 - 7	8 - 15	16 - 19	>20
Predicted lifetime hospitalisation discounted cost (£): base case	**132,375**	**126,717**	**127,327**	**134,987**	**118,322**	**111,706**	**112,841**	**110,608**
95% credible interval	(131,007-133,744)	(125,488-127,947)	(126,119-128,536)	(133,737-136,238)	(117,106-119,538)	(110,581-112,831)	(111,745-113,936)	(109,602-111,614)
Predicted lifetime hospitalisation discounted cost (£): intervention*	**130,878**	**125,527**	**124,474**	**125,271**	**117,278**	**110,768**	**110,665**	**104,426**
95% credible interval	(129,521-132,235)	(124,273-126,782)	(123,244-125,705)	(123,994-126,549)	(116,071-118,486)	(109,617-111,919)	(109,538-111,793)	(103,384-105,468)

*The results of intervention demonstrate that intervention would result in the stoppage of drinking and smoking for all groups.
Note: The results were derived from a probabilistic model using 5,000 simulations. BMI, SIMD, CVD, diabetes, prior hospitalisation, and GHQ score were varied for baseline risk profiles but not presented.

Table 8-5 Predicted remaining lifetime hospitalisation discounted cost compared between the base-case and the intervention classified by risks profiles: males (cont.)

Age (years)	**40**				**50**			
Base case modifiable risk factors								
Drinking status	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence
AUDIT score	0 - 7	8 - 15	16 - 19	>20	0 - 7	8 - 15	16 - 19	>20
Predicted lifetime hospitalisation discounted cost (£): base case	**97,382**	**98,943**	**87,331**	**90,259**	**75,747**	**75,661**	**76,115**	**78,329**
95% credible interval	(96,398-98,367)	(97,948-99,939)	(85,448-89,215)	(89,434-91,084)	(75,009-76,485)	(74,911-76,411)	(75,381-76,848)	(77,610-79,048)
Predicted lifetime hospitalisation discounted cost (£): intervention*	**98,746**	**99,080**	**85,859**	**85,370**	**75,440**	**75,576**	**75,463**	**75,763**
95% credible interval	(97,737-99,756)	(98,063-100,097)	(83,995-87,723)	(84,517-86,222)	(74,696-76,185)	(74,808-76,344)	(74,709-76,217)	(75,014-76,513)

*The results of intervention demonstrate that the intervention would result in the stoppage of drinking and smoking for all groups.
Note: The results were derived from a probabilistic model using 5,000 simulations. BMI, SIMD, CVD, diabetes, prior hospitalisation, and GHQ score were varied for baseline risk profiles but not presented.

Table 8-6 Predicted remaining lifetime hospitalisation discounted cost compared between the base-case and the intervention classified by risks profiles: females

Age (years)	**20**				**30**			
Base case modifiable risk factors								
Drinking status	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence
AUDIT score	0-4	5-12	13-16	>17	0-4	5-12	13-16	>17
Predicted lifetime hospitalisation discounted cost (£): base case	**276,050**	**271,291**	**252,345**	**257,047**	**243,969**	**209,984**	**210,550**	**208,911**
95% credible interval	(272,981-279119)	(268,643-273,938)	(250,312-254,378)	(254,543-259,550)	(230,686-257,252)	(207,900-212,068)	(207,877-213,224)	(206,098-211,725)
Predicted lifetime hospitalisation discounted cost (£): intervention*	**275,633**	**274,085**	**255,324**	**257,703**	**241,816**	**211,535**	**210,733**	**210,872**
95% credible interval	(187,815-192,904)	(186,333-192,730)	(188,389-191,568)	(159,659-162,525)	(128,716-130,624)	(134,280-140,653)	(135,695-140,230)	(133,975-137,459)

*The results of intervention demonstrate that intervention would result in the stoppage of drinking and smoking for all groups.
Note: The results were derived from a probabilistic model using 5,000 simulations. BMI, SIMD, CVD, diabetes, prior hospitalisation, and GHQ score were varied for baseline risk profiles but not presented.

Table 8-6 Predicted remaining lifetime hospitalisation discounted cost compared between the base-case and the intervention classified by risks profiles: females (cont.)

Age (years)	**40**				**50**			
Base case modifiable risk factors								
Drinking status	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence	low-risk drinking	hazardous drinking	harmful drinking	possible alcohol dependence
AUDIT score	0-4	5-12	13-16	>17	0-4	5-12	13-16	>17
Predicted lifetime hospitalisation discounted cost (£): base case	**191,114**	**189,256**	**189,033**	**164,616**	**129,708**	**140,199**	**140,078**	**139,732**
95% credible interval	(272,981-279,119)	(268,643-273,938)	(250,312-254,378)	(254,543-259,550)	(230,686-257,252)	(207,900-212,068)	(207,877-213,224)	(206,098-211,725)
Predicted lifetime hospitalisation discounted cost (£): intervention*	**190,359**	**189,532**	**189,978**	**161,092**	**129,670**	**137,467**	**137,962**	**135,717**
95% credible interval	(187,815-192,904)	(186,333-192,730)	(188,389-191,568)	(159,659-162,525)	(128,716-130,624)	(134,280-140,653)	(135,695-140,230)	(133,975-137,459)

*The results of intervention demonstrate that intervention would result in the stoppage of drinking and smoking for all groups.
Note: The results were derived from a probabilistic model using 5,000 simulations. BMI, SIMD, CVD, diabetes, prior hospitalisation, and GHQ score were varied for baseline risk profiles but not presented.

8.3.2 Uncertainty analysis

Cost-effectiveness plane

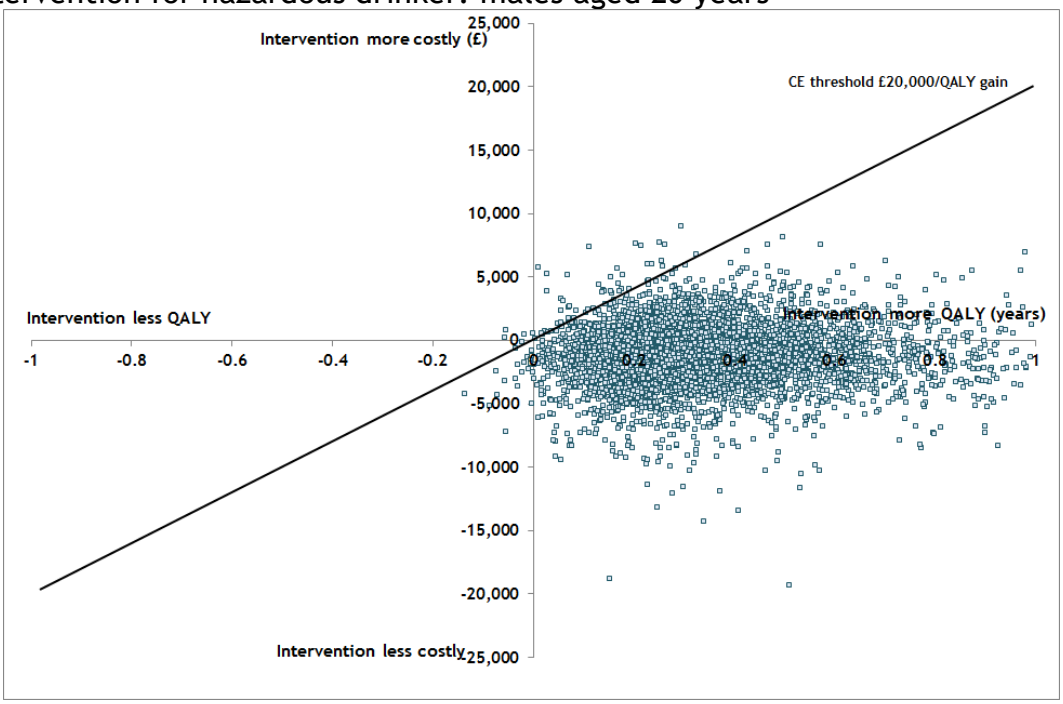
To take account of the uncertainty of input parameters which could impact the uncertainty of cost-effectiveness outputs, the PSA was performed using Monte Carlo simulations. Then, the results were presented via scatter plots of the 5,000 iterations on a cost-effectiveness plane as shown in Figure 8-2 to Figure 8-9. These results demonstrate the intervention that aimed to stop smoking and drinking at a hazardous level (AUDIT score of 7-15 for males and 5-12 for females) in ages 20, 30, 40 and 50 years and classified by gender. For males (as shown in Figure 8-2 to Figure 8-5), considering where the data points are located on the cost-effectiveness plane, it can be seen that the majority of these data points are in either the southeast quadrant that - suggesting the intervention would be dominant (cost-saving and increased effectiveness) especially in the younger ages, or the northeast quadrant (i.e. the intervention yielded more QALYs but at a higher cost) and located below the threshold of £20,000/QALY gained.

For females (Figure 8-6 to Figure 8-9), the scatter plots appear less precise than the plots for males since the input parameters used for the female model indicated higher uncertainty. The overall results showed that the intervention for stopping hazardous drinking and smoking for females would be less cost-effective compared to males. For females aged 20 and 30 years (Figure 8-6 and Figure 8-7), the majority of the data points shown on the cost-effectiveness plane are in the northeast quadrant and a small proportion of data points are in either the southeast quadrant or northwest quadrant (i.e. the intervention is yielded less QALYs but at a higher cost referred as dominated by the base-case). When comparing the ICER simulations (data points) to the cost-effectiveness threshold of £20,000, approximately half of these data points were below the threshold. For older cohort aged 40 and 50 years (Figure 8-8 and Figure 8-9), the majority of these data points appeared in either the northeast quadrant and over the threshold or northwest quadrant. This might suggest that the intervention for females of older ages would be unlikely cost-effective due to higher costs and less QALY gained.

Cost-effectiveness acceptability curve

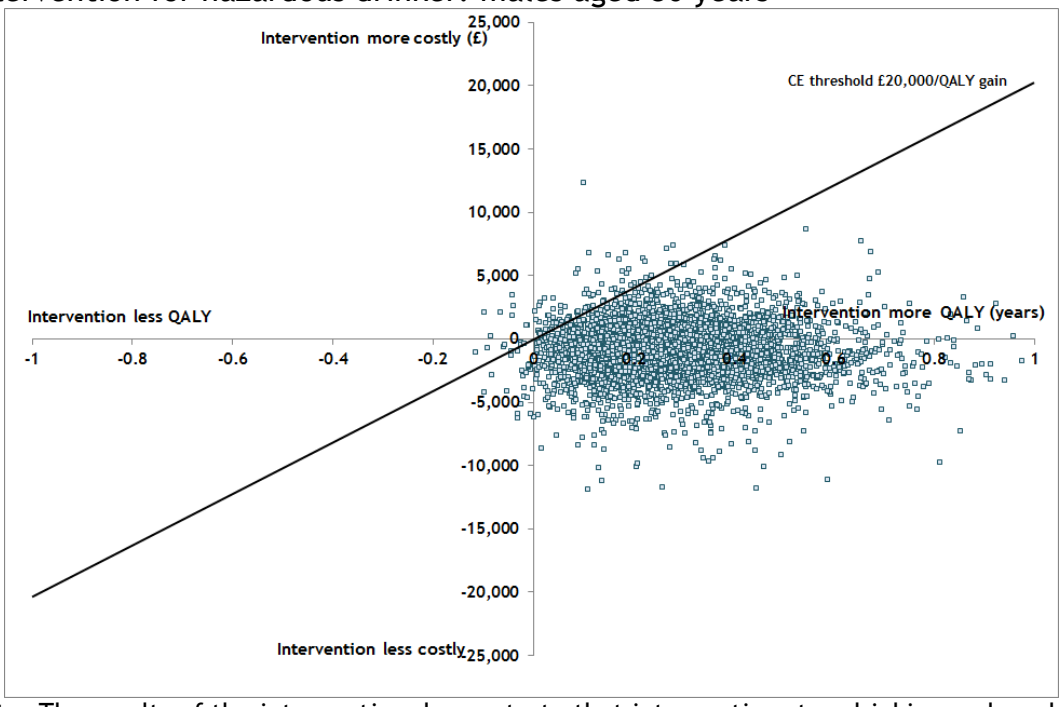
Figure 8-10 to Figure 8-17 present the CEAC to show the probability of either the hypothetical intervention or base case being cost-effectiveness at different ceiling thresholds ranging from £0 to £240,000, with the dashed line representing the threshold of £20,000/QALY gained. In the same manner, the target population for the intervention was hazardous drinkers (measured by the AUDIT) combined with other risk profiles (e.g. smoking) at ages 20, 30, 40, and 50 years classified by gender, and the intervention aimed to stop alcohol drinking as well as smoking. For males (Figure 8-10 to Figure 8-13), the results plotted on the cost-effectiveness plane showed that the probability of the intervention being cost-effective at the threshold of £20,000/QALY gained was over 95% as compared to less than 5% for the base-case. For females, the probability of the intervention being cost-effective was around 60% for those aged 20 years (Figure 8-14) as compared to 40% for the base-case. Nevertheless, for females of older age (30, 40, and 50 years), the probabilities of the intervention being cost-effective were lower than 40% (as shown in Figure 8-15 to Figure 8-17).

Figure 8-2 Scatterplot on the cost-effectiveness plane: base-case vs. intervention for hazardous drinker: males aged 20 years



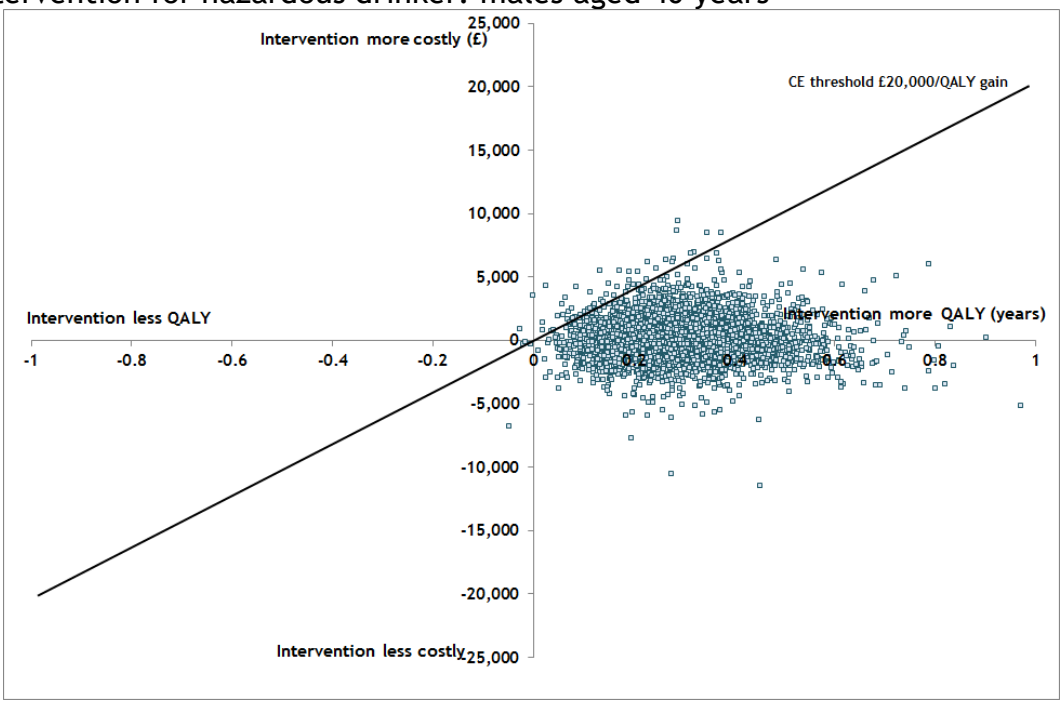
Note: The results of the intervention demonstrate that intervention would stop drinking and smoking for base-case risk profiles: males, aged 20 years, AUDIT score=15 (hazardous drinker), binge drinking, normal BMI, no CVD, no diabetes, 5 cigarettes per day, high physical activity, 4th SIMD, prior hospitalisation over last year, and best GHQ score.

Figure 8-3 Scatterplot on the cost-effectiveness plane: base-case vs. intervention for hazardous drinker: males aged 30 years



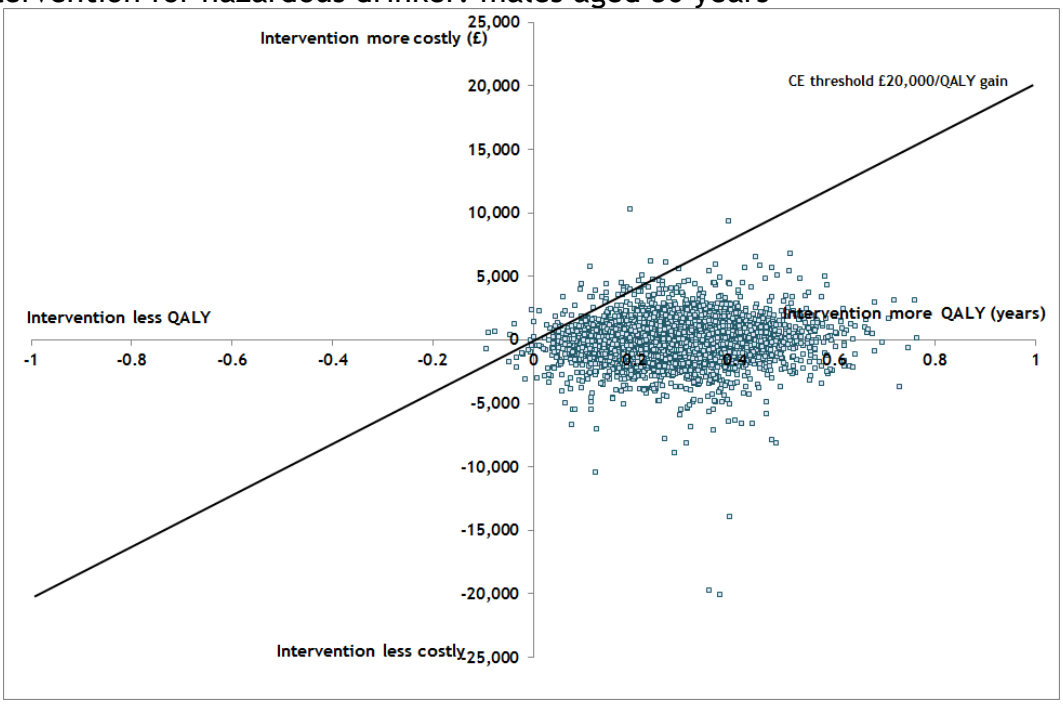
Note: The results of the intervention demonstrate that intervention stop drinking and smoking for base-case risk profiles: males, aged 30 years, AUDIT score=15 (hazardous drinker), binge drinking, overweight, no CVD, no diabetes, 5 cigarettes per day, high physical activity, 4th SIMD, prior hospitalisation over last year, and best GHQ score.

Figure 8-4 Scatterplot on the cost-effectiveness plane: base-case vs. intervention for hazardous drinker: males aged 40 years



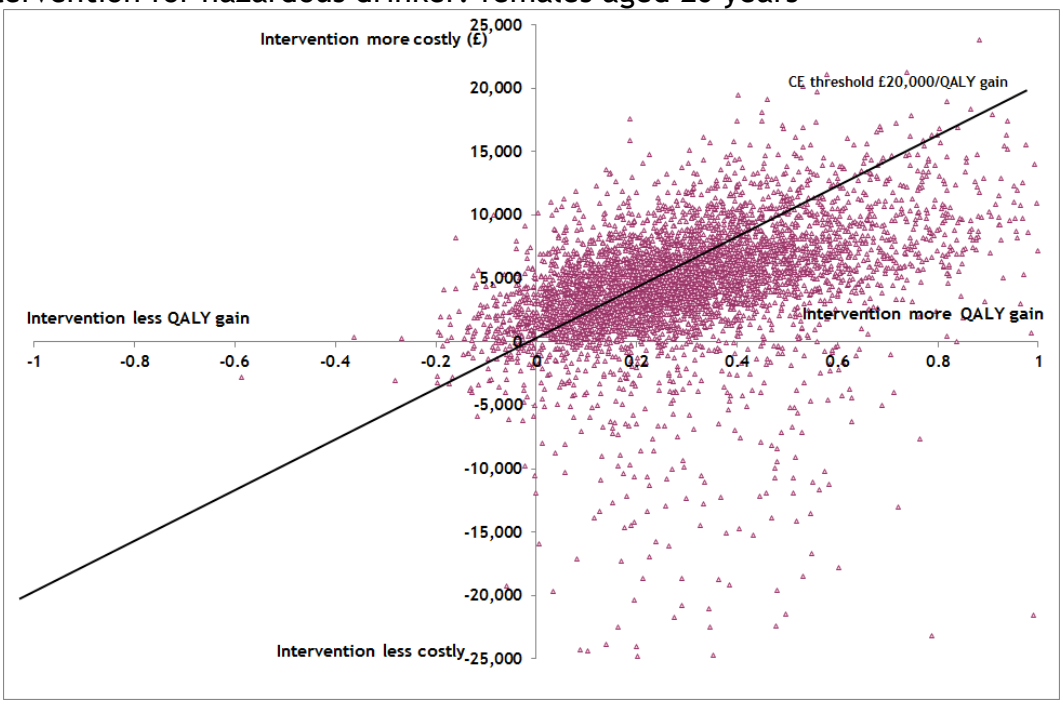
Note: The results of the intervention demonstrate that intervention would stop drinking and smoking for base case risk profiles: males, aged 40 years, AUDIT score=15 (hazardous drinker), binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, high physical activity, 2nd SIMD, prior hospitalisation over last year, and best GHQ score.

Figure 8-5 Scatterplot on the cost-effectiveness plane: base-case vs. intervention for hazardous drinker: males aged 50 years



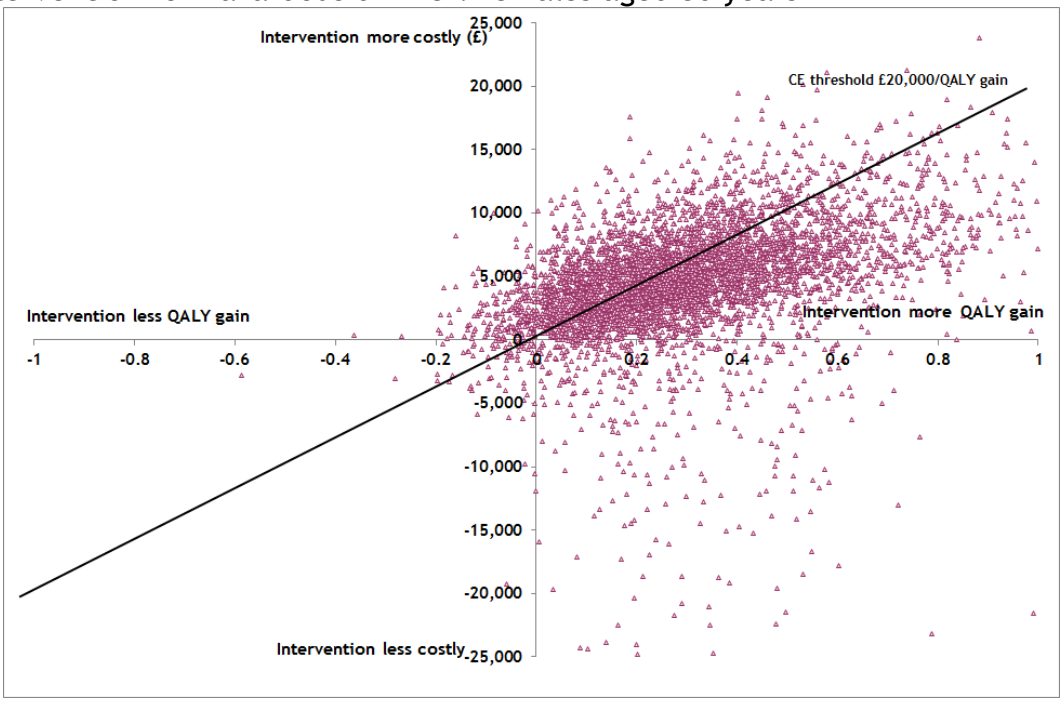
Note: The results of intervention demonstrate that the intervention would stop drinking and smoking for base-case risk profiles: males, aged 50 years, AUDIT score=15 (hazardous drinker), binge drinking, overweight, having CVD, no diabetes, 6 cigarettes per day, medium physical activity, 2nd SIMD, prior hospitalisation over last year, and best GHQ score.

Figure 8-6 Scatterplot on the cost-effectiveness plane: base-case vs. intervention for hazardous drinker: females aged 20 years



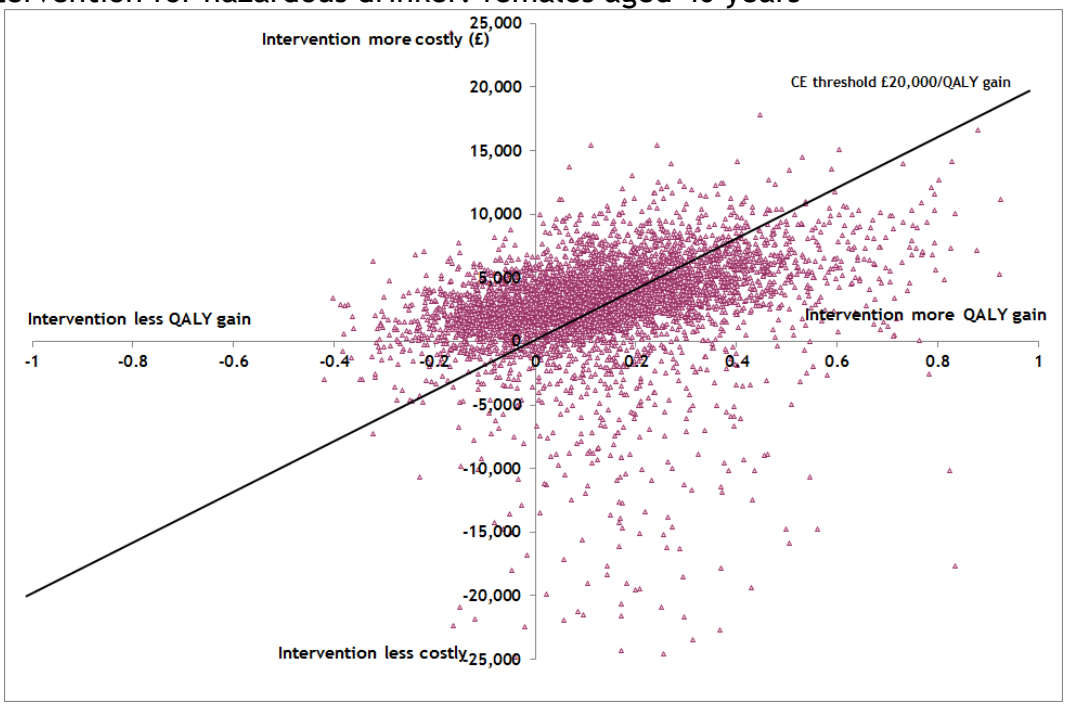
Note: The results of the intervention demonstrate that intervention would stop drinking and smoking for base case risk profiles: females, aged 20 years, AUDIT score=12 (hazardous drinker), binge drinking, normal BMI, no CVD, no diabetes, 5 cigarettes per day, medium physical activity, 4th SIMD, prior hospitalisation over last year, and best GHQ score.

Figure 8-7 Scatterplot on the cost-effectiveness plane: base-case vs. intervention for hazardous drinker: females aged 30 years



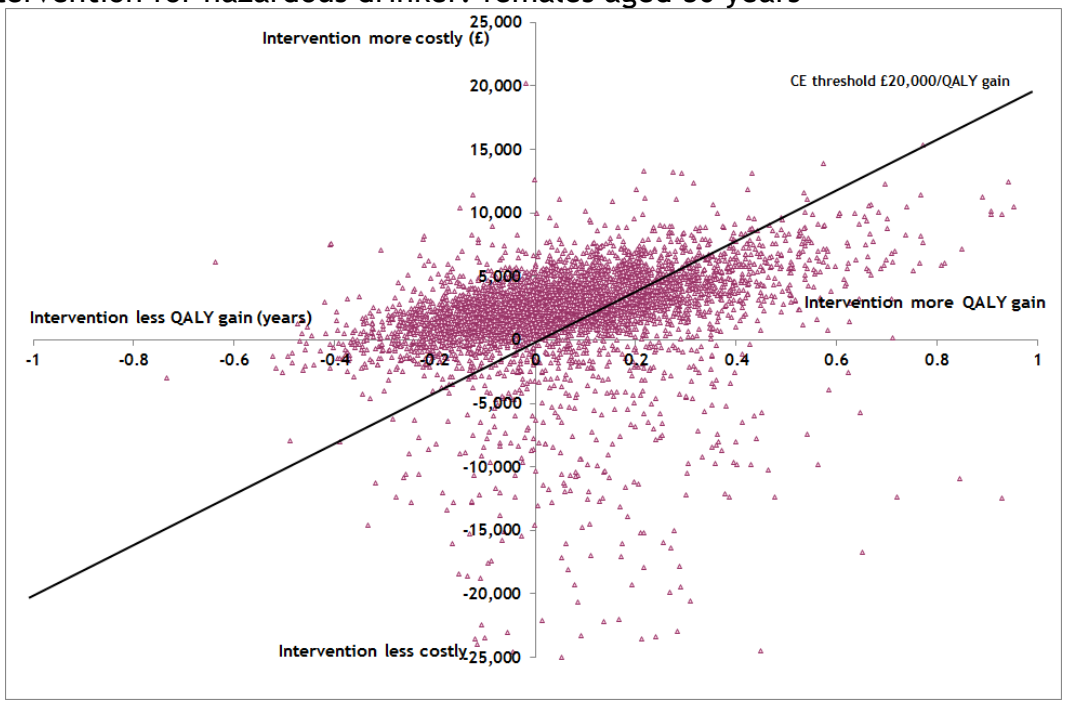
Note: The results of the intervention demonstrate that intervention would stop drinking and smoking for base case risk profiles: females, aged 30 years, AUDIT score=12 (hazardous drinker), binge drinking, overweight, no CVD, no diabetes, 5 cigarettes per day, medium physical activity, 5th SIMD, prior hospitalisation over last year, and best GHQ score.

Figure 8-8 Scatterplot on the cost-effectiveness plane: base-case vs. intervention for hazardous drinker: females aged 40 years



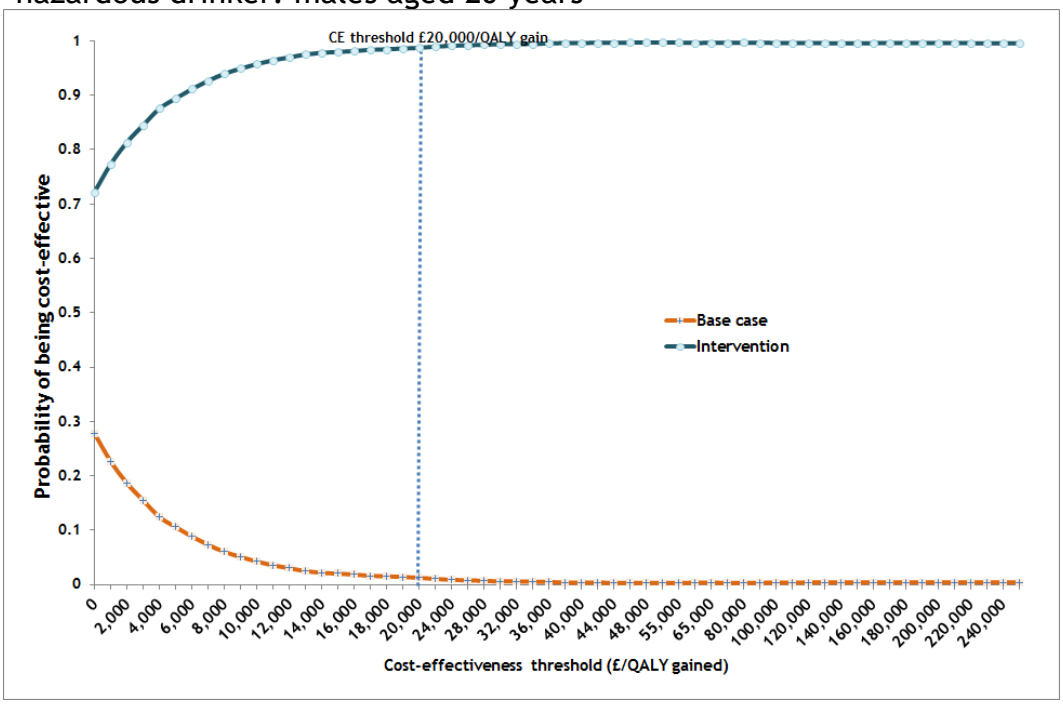
Note: The results of the intervention demonstrate that the intervention would stop drinking and smoking for base-case risk profiles: females, aged 40 years, AUDIT score=12 (hazardous drinker), binge drinking, overweight, no CVD, no diabetes, 5 cigarettes per day, high physical activity, 2nd SIMD, prior hospitalisation over last year, and best GHQ score.

Figure 8-9 Scatterplot on the cost-effectiveness plane: base-case vs. intervention for hazardous drinker: females aged 50 years



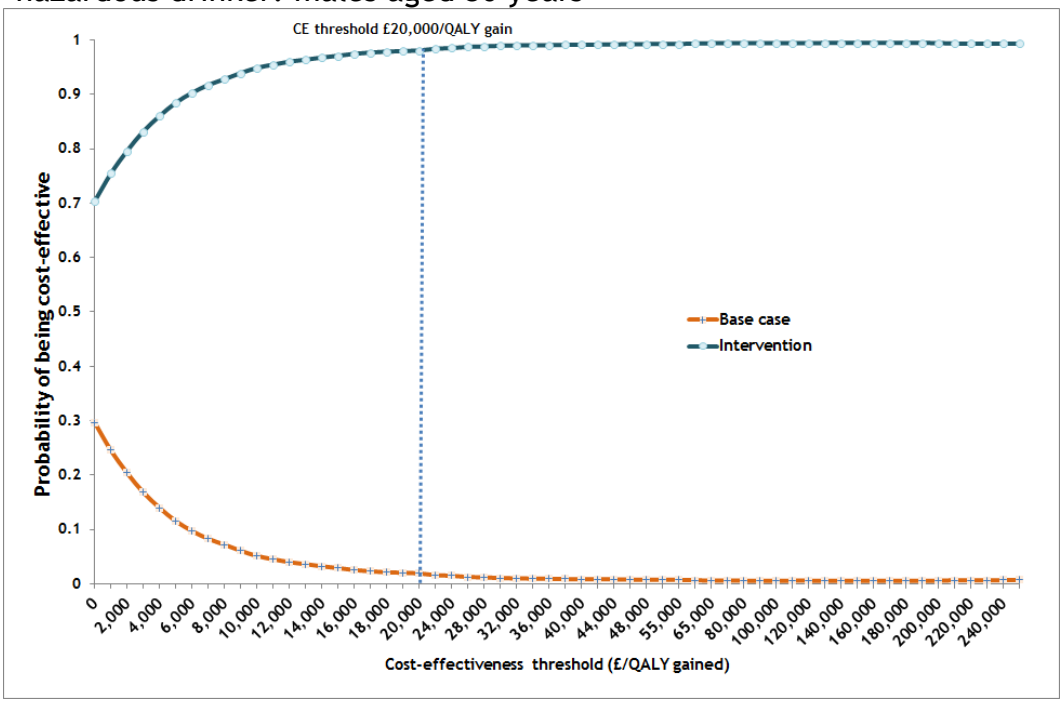
Note: The results of the intervention demonstrate that intervention would stop drinking and smoking for base-case risk profiles: females, aged 50 years, AUDIT score=12 (hazardous drinker), binge drinking, overweight, having CVD, no diabetes, 4 cigarettes per day, no physical activity, 2nd SIMD, prior hospitalisation over last year, and best GHQ score.

Figure 8-10 Cost-effectiveness acceptability curve: base-case vs. intervention for hazardous drinker: males aged 20 years



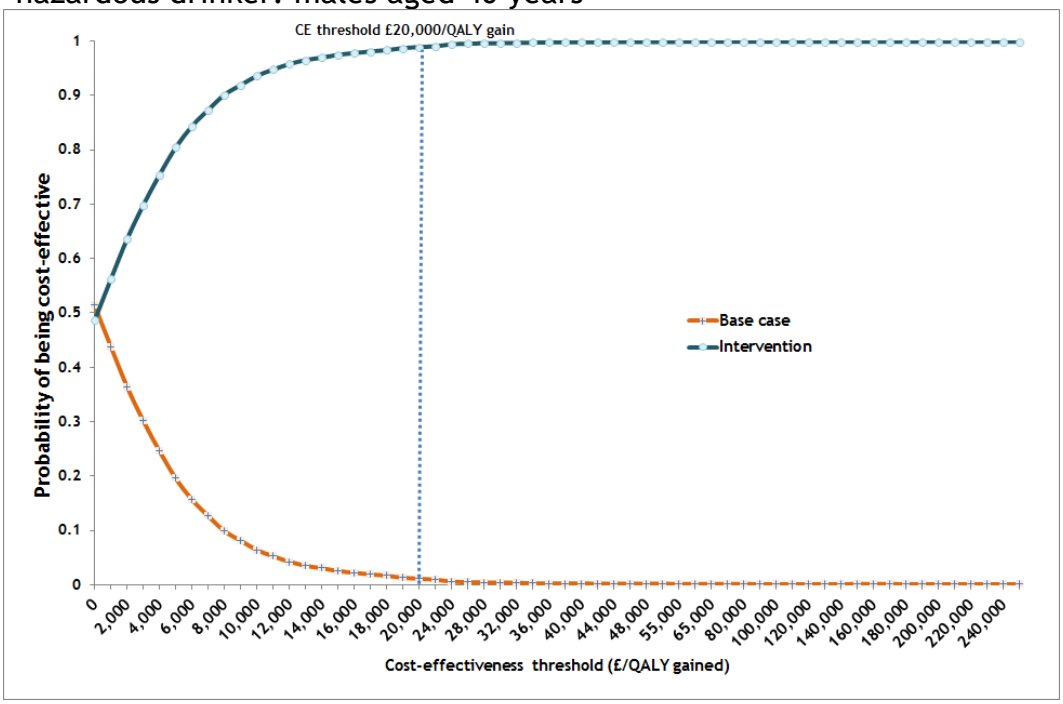
Note: The results of the intervention demonstrate that intervention would stop drinking and smoking for base-case risk profiles: males, aged 20 years, AUDIT score=15 (hazardous drinker), binge drinking, normal BMI, no CVD, no diabetes, 5 cigarettes per day, high physical activity, 4th SIMD, prior hospitalisation over last year, and best GHQ score.

Figure 8-11 Cost-effectiveness acceptability curve: base-case vs. intervention for hazardous drinker: males aged 30 years



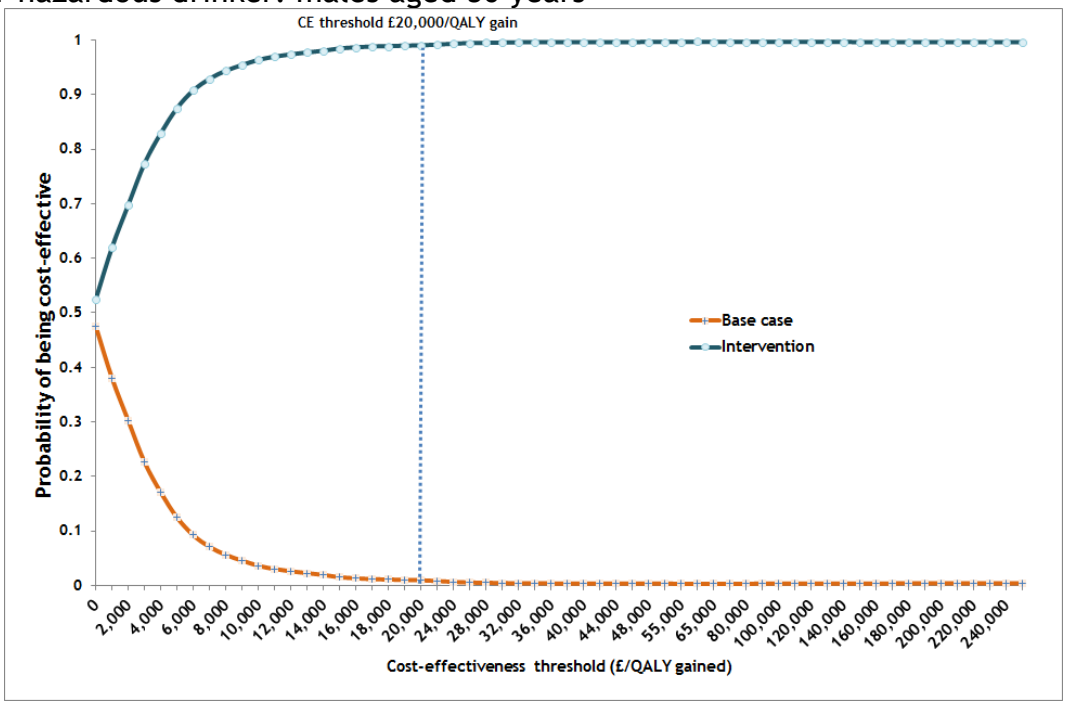
Note: The results of the intervention demonstrate that intervention would stop drinking and smoking for base-case risk profiles: males, aged 30 years, AUDIT score=15 (hazardous drinker), binge drinking, overweight, no CVD, no diabetes, 5 cigarettes per day, high physical activity, 4th SIMD, prior hospitalisation over last year, and best GHQ score.

Figure 8-12 Cost-effectiveness acceptability curve: base-case vs. intervention for hazardous drinker: males aged 40 years



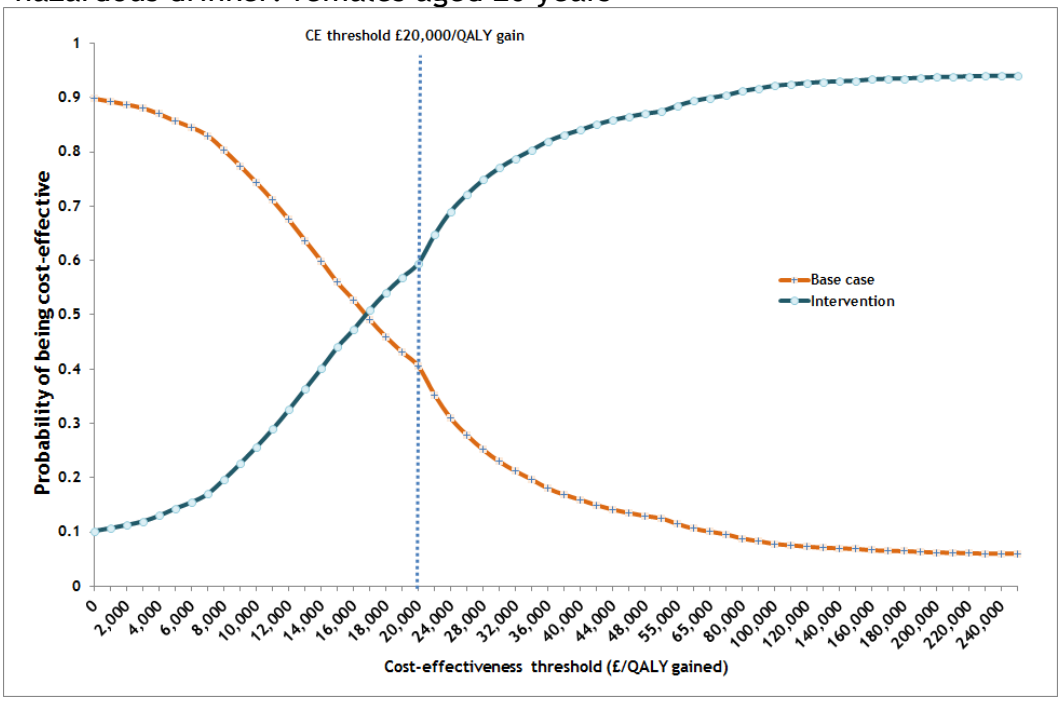
Note: The results of the intervention demonstrate that intervention would stop drinking and smoking for base case risk profiles: males, aged 40 years, AUDIT score=15 (hazardous drinker), binge drinking, overweight, no CVD, no diabetes, 6 cigarettes per day, high physical activity, 2nd SIMD, prior hospitalisation over last year, and best GHQ score.

Figure 8-13 Cost-effectiveness acceptability curve: base-case vs. intervention for hazardous drinker: males aged 50 years



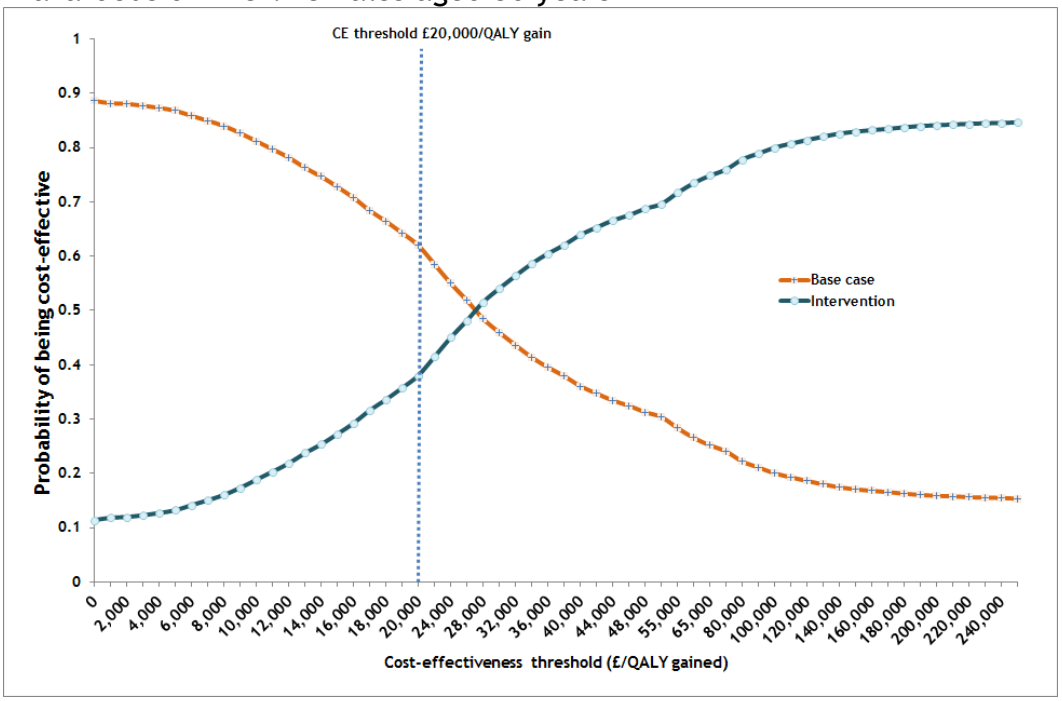
Note: The results of the intervention demonstrate that intervention would stop drinking and smoking for base-case risk profiles: males, aged 50 years, AUDIT score=15 (hazardous drinker), binge drinking, overweight, having CVD, no diabetes, 6 cigarettes per day, medium physical activity, 2nd SIMD, prior hospitalisation over last year, and best GHQ score.

Figure 8-14 Cost-effectiveness acceptability curve: base-case vs. intervention for hazardous drinker: females aged 20 years



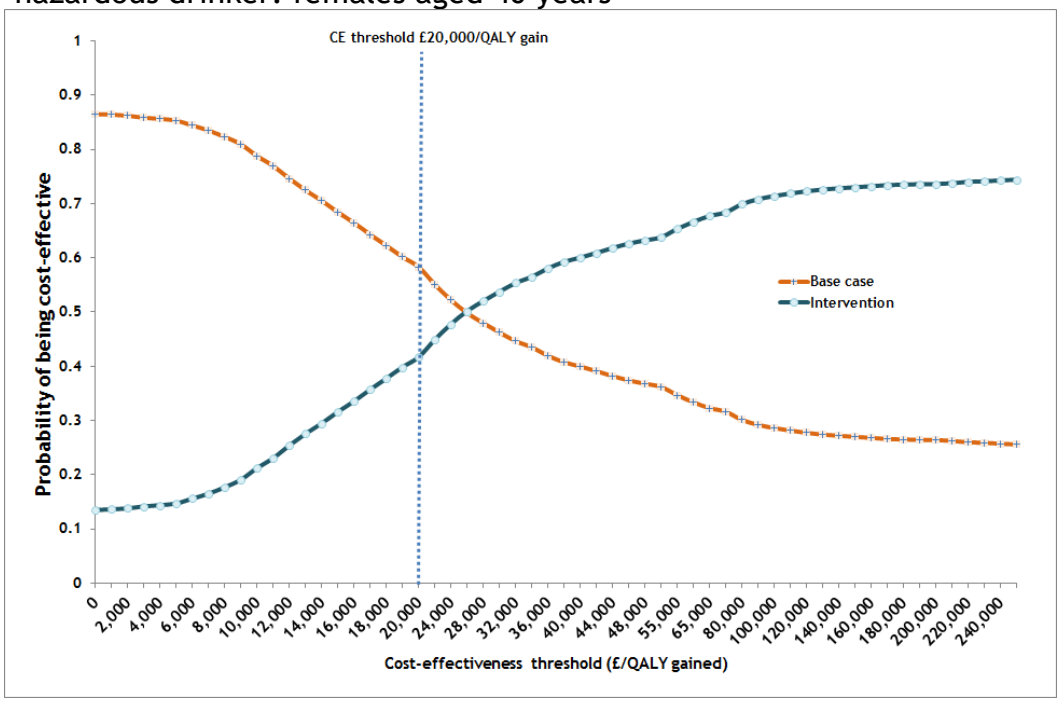
Note: The results of the intervention demonstrate that intervention would stop drinking and smoking for base case risk profiles: females, aged 20 years, AUDIT score=12 (hazardous drinker), binge drinking, normal BMI, no CVD, no diabetes, 5 cigarettes per day, medium physical activity, 4th SIMD, prior hospitalisation over last year, and best GHQ score.

Figure 8-15 Cost-effectiveness acceptability curve: base-case vs. intervention for hazardous drinker: females aged 30 years



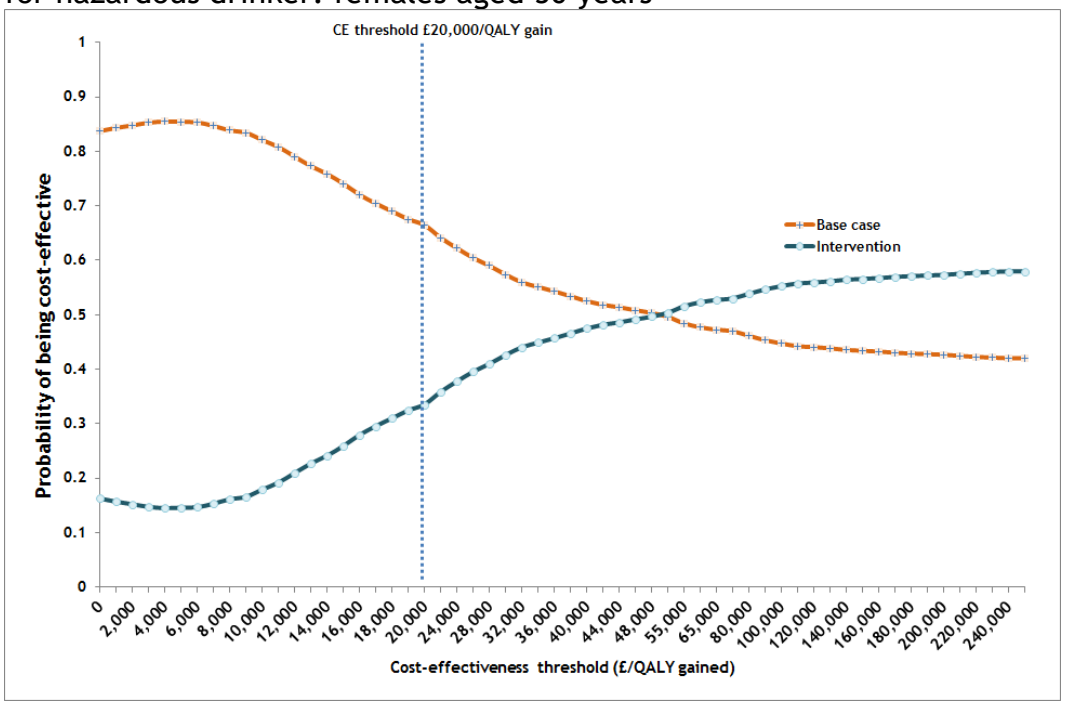
Note: The results of the intervention demonstrate that intervention would stop drinking and smoking for base-case risk profiles: females, aged 30 years, AUDIT score=12 (hazardous drinker), binge drinking, overweight, no CVD, no diabetes, 5 cigarettes per day, medium physical activity, 5th SIMD, prior hospitalisation over last year, and best GHQ score.

Figure 8-16 Cost-effectiveness acceptability curve: base-case vs. intervention for hazardous drinker: females aged 40 years



Note: The results of the intervention demonstrate that intervention would stop drinking and smoking for base-case risk profiles: females, aged 40 years, AUDIT score=12 (hazardous drinker), binge drinking, overweight, no CVD, no diabetes, 5 cigarettes per day, high physical activity, 2nd SIMD, prior hospitalisation over last year, and best GHQ score.

Figure 8-17 Cost-effectiveness acceptability curve: base-case vs. intervention for hazardous drinker: females aged 50 years



Note: The results of the intervention demonstrate that intervention would stop drinking and smoking for base case risk profiles: females, aged 50 years, AUDIT score=12 (hazardous drinker), binge drinking, overweight, having CVD, no diabetes, 4 cigarettes per day, no physical activity, 2nd SIMD, prior hospitalisation over last year, and best GHQ score.

8.4 Discussion

The economic evaluation shown compared the no intervention case with the hypothetical health promotion intervention. The hypothetical intervention of this analysis aimed to change drinking (measured by the AUDIT) and smoking (measured by the number of cigarette per day) behaviours so the cohorts quit, whereas other selected risk factors (e.g. SIMD, physical activity, and BMI) were assumed to be the same as the baseline. Comparing the costs and benefits of new intervention and control over the lifetime period, a within-trial analysis combined with the developed model was able to capture both short- and longer-term consequences to estimate the cost-effectiveness of the intervention. This study developed the structure of the analysis model and specified the input parameters needed to conduct further cost-effectiveness analyses of other health promotion interventions. Finally, the presented cost-effectiveness results were shown using a probabilistic model, which accounted for parameter uncertainty, and the results were compared to the cost-effective threshold of the UK (£20,000 per QALY gained). Moreover, the cost-effectiveness results were sub-grouped by age, gender, and different risk factors so they can inform the policy decision-making process on defining target groups of the intervention based on cost-effectiveness information.

The previous studies conducted an economic evaluation of an alcohol intervention alongside RCTs with a short-term follow-up period by using a modelling approach to extrapolate the costs and outcomes beyond the end-of-trial for the lifetime horizon (Barbosa et al., 2010b, Purshouse et al., 2013, Barbosa et al., 2015, Cowell et al., 2010, Navarro et al., 2011, Tariq et al., 2009). Most of modelling studies evaluated the cost-effectiveness of screening and brief intervention (SBI) for alcohol use disorder (Barbosa et al., 2015, Cowell et al., 2010, Purshouse et al., 2013, Angus et al., 2014b). The results showed the SBI's efficacy in terms of reducing alcohol drinking problems, and it was also reported in many systematic reviews and meta-analyses (Bray et al., 2011, Donoghue et al., 2014, Fachini et al., 2012, Babor et al., 2007). Those studies examined the relationships between SBI and changes in consumption

and/or alcohol-related harms within the follow-up period; the changes in consumption level were then modelled to estimate the changes of alcohol-related diseases and/or other harms over time.

The estimated QALYs from this study may not be directly comparable to other studies because of the differences in modelling methods, utility measurement, and defined drinking status; however, there is an only one UK study where the QALYs of harmful drinking (defined as grams of alcohol consumption per day) may be compared with the QALYs of this study (Barbosa et al., 2010a). Discounted QALYs derived from the UK study was 12.98 years (male cohort aged 40 years with harmful drinking defined as alcohol consumption ≥80 g/day) while discounted QALYs of the current model was 16.36 years for male aged 40 years with an AUDIT score of 16-19, i.e. harmful drinking. The approximately three-year difference between the two studies may be due to the difference in the utility measurement tool; the previous study obtained its utility value from the EQ-5D while this study used the SF-12 (SF-6D). Moreover, Barbosa et.al. applied a discounting rate of 3.5% per year following previous NICE recommendations (National Institute for Clinical Excellence (NICE), 2004), whereas this study followed a later recommendation specific to public health interventions and utilised a discounting rate of 1.5% per year (National Institute for Health and Care Excellence (NICE), 2012).

However, this current study is the first one that measured the outcome measurement of an alcohol intervention using the AUDIT. The AUDIT was chosen because it can capture the range of alcohol drinking problems by assessing 10 categories and computing a score between 0-40 for a final drinking problem assessment, and it has been widely used for alcohol drinking problem screening before provided brief intervention (as described in Chapter 4). Other issues of those existing models are the limited number of drinking states and alcohol-related problems within the study cohort, e.g. absenteeism, moderate-risk consumption, high-risk consumption (Barbosa et al., 2015, Barbosa et al., 2010b, Purshouse et al., 2013, Cobiac et al., 2009). In addition, the cut-off for classifying high-risk alcohol consumption as a drinking state is likely to change

in the future so this would limit the application of existing alcohol models which used different cut-off values of drinking states. Moreover, the existing studies modelled long-term health consequences including alcohol-related conditions but the range of included diseases may not cover all the possible conditions that may cause an underestimation of the results (Barbosa et al., 2015, Barbosa et al., 2010b, Purshouse et al., 2013, Cobiac et al., 2009).

The most recent systematic review reported the cost-effectiveness of SBIs for alcohol misuse in the primary care setting, and almost all the studies suggested that SBIs were cost-effective (Angus et al., 2014a). However, this systematic review found that there was heterogeneity in the methods of the included studies such as estimated costs and health outcomes. As such, results obtained from this model in other settings might be invalid due to transferability issues. Moreover, 22 of the 23 studies were conducted in high-income countries so there is still a lack of evidence in low- and middle-income countries which may have substantial heterogeneity compared to high-income countries due to the local context and limited resources (Angus et al., 2014a). It can be seen that the cost-effectiveness results of the alcohol intervention were less transferable to other settings. Further studies should be conducted regarding methodological transferability, especially in the low- and middle-income country context (as demonstrated in Chapter 9).

As recommended by the economic evaluation for public health guidelines (Weatherly et al., 2009), the research should consider health inequality, e.g. the effectiveness of an intervention among different socio-economic status and/or individual health risk. The effectiveness study evaluated the effects of minimum unit pricing for alcohol in the UK on different income and socioeconomic groups (Holmes et al., 2014a). However, the measured primary outcome was the percentage change of consumption classified into moderate, hazardous, and harmful drinkers in different income quintiles, and drinking patterns - which were an intermediate outcome - were then modelled using morbidity and mortality risks classified by those drinkers. Therefore, long-term inequality would not be tackled if the interventions found that there were

different effects on the hospitalisations and deaths of drinkers who were of different socioeconomic status and other risk behaviours (Jones and Bellis, 2014, Probst et al., 2014, Probst et al., 2015b).

Although the current analytical framework has successfully demonstrated the cost-effectiveness analysis of this health promotion intervention, it has certain limitations. Firstly, the SIMD quintile was selected to be the measurement of socioeconomic status in order to investigate health inequality among the Scottish population. As such, this index cannot be applied to other settings; further research in other countries will need to explore the standard tool used for socioeconomic status assessment in their context. Secondly, the estimated costs of the study captured, particularly the healthcare costs of drinkers, would underestimate the total lifetime costs and the costs of other people affected by the drinkers. The societal perspective should be used to account for the wider impacts of alcohol consumption on society as a whole. Thirdly, The cost-effectiveness result of study accounted for parameter uncertainty using PSA as well as heterogeneity of risk profiles (e.g. drinking, smoking and BMI), while other uncertainties have been presented in the majority of models; the type of model, model structure, and method use (Briggs, 2000). These uncertainties were dealt with the different approaches (Appendix 8). The reference case for appropriate methodology can be used for methodological uncertainties i.e. by following good practice guidelines for undertaking modelling (ISPOR, 2014). Uncertainty regarding the structure of the model can be dealt with by one-way sensitivity analyses and scenario analyses, modifying one or more structural aspects or assumptions of the model and determining the impact on outcomes (Bojke et al., 2009). Thus, a further study should concern other types of uncertainty which would likely affect an intervention cost-effectiveness. Finally, the hypothetical intervention assumed the best-case scenario that the intervention would result in no more drinking and smoking in the first year of implementation, and then all participants would receive this intervention every year to maintain their risk behaviours same as in the first year. To simplify the demonstration of the model, a coverage rate and acceptance rate of 100% were applied in the

analysis. Thus, further studies should consider all required input parameters to quantify the effectiveness of the intervention under evaluation.

8.5 Conclusions

Using the analysis framework for cost-effectiveness of the health promotion intervention, not only was an alcohol intervention evaluation performed - which was the main analysis of the model - but it was also combined with other modified risk behaviours such as smoking cessation to reduce multiple unhealthy behaviours that was suggested to be more effective than a single targeted behaviour change.

Chapter 9: Methodological transferability of developing a health promotion model for economic evaluation in Thailand: a case study of alcohol control interventions

9.1 Introduction

9.1.1 Health-related risk behaviour and health promotion interventions in Thailand

The magnitude of chronic non-communicable diseases (NCDs) has been gradually increasing in Thailand (Kaufman et al., 2011). In 2013, the major diseases that cause death in some Thais as well as years of good health for other were NDCs, e.g. stroke, ischemic heart disease (IHD), diabetes, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), or liver cancer (Livingston and Callinan, 2015). These diseases contributed to more than 70% of Thai deaths in 2014, equivalent to approximately more than 350,000 deaths per year (WHO, 2014). Many studies have shown the link between precarious lifestyles and NCDs - which driven primarily by four major risk factors: tobacco use, physical inactivity, the harmful use of alcohol and unhealthy diets (Doll et al., 2004, N.C.D. Risk Factor Collaboration, 2016, Parry et al., 2011, Thakur et al., 2011, Wakabayashi et al., 2015, Webber et al., 2012). For instance, the data in 2010 showed that Thai males consumed approximately 14 litres of pure alcohol per year. Additionally, 50 per cent of Thai males also smoked in 2011 (WHO, 2014).

Health promotion has become an interesting issues since 1986, where it was defined as “a process of enabling people to increase control over, and to improve, their health”(WHO, 2014). Health promotion was recommended as an effective approach for decreasing and preventing NCDs (International Union for Health Promotion and Education, 2011). In Thailand, health promotion has been developed and implemented for over a decade. The tobacco control movement

in Thailand became a global example in advocacy to establish policies, legislation and regulation to reduce and ultimately prevent the consumption of cigarettes (Galbally et al., 2012). In 2001, the Thai Health Promotion Foundation (ThaiHealth) was established to promote and increase a healthy life for Thai people by using multiple approaches: increasing tobacco and alcohol taxes, promoting a healthy sponsorship of sports and culture, developing healthy environments, developing multi-sectoral support for health promotion, taking a social determinants approach, and promoting innovation and new knowledge. In the past decade, ThaiHealth and partner organisations were able to modify major health risk factors (e.g. alcohol and tobacco consumption, and road accidents) through a wide range of interventions (Galbally et al., 2012), e.g. increasing the excise tax of tobacco and alcoholic beverages, the Tobacco Control Act and Alcohol Control Act, drink-driving countermeasures and increased penalties, controlling accessibility, reducing underage smoking and drinking, banning advertisement and social marketing such as the annual "No alcohol during Buddhist Lent" campaign for the 3-month period, and Road Safety Campaigns during annual festivals.

9.1.2 Alcohol consumption and alcohol-related death in Thailand compared to the UK

Alcohol consumption in Thailand has increased steadily since 1990 leading to the higher magnitude of alcohol-related problems comparing South-East Asia countries (WHO, 2014). Table 9-1 presents a comparison of alcohol consumption measured by the AUDIT score among Thailand, Scotland, and England. In 2015, the Scottish Health Survey on alcohol consumption reported hazardous and harmful levels of drinking (measured by weekly unit consumption) for 36% of men and 17% of women (Gray and Leyland, 2015). The proportion of binge drinking (drinking more than 8 units for men and 6 units for women) on the heaviest drinking day were 32% and 14% of men and women, respectively. Using the AUDIT measurement, the majority of SHeS participants (75% for males and 88% for females) were classified as low-risk drinkers. Meanwhile, SHeS participants with alcohol use disorders (i.e. hazardous

drinker, harmful drinker, and possible alcohol dependence) comprised 25% and 12% for males and females, respectively.

According to the Adult Psychiatric Morbidity Survey and Health Survey 2014, most adults in England aged 16-64 drank at lower risk levels based on the AUDIT measurement (72% of men and 85% of women). About 23% of men and 13% of women drank at hazardous levels, and 5% of men and 2% of women were harmful drinkers and possibly alcohol dependent (Drummond et al., 2016). The prevalence of drinking at harmful or dependent levels was highest among young adults -particularly men aged 25–34 and women aged 16–24 - but this declined gradually with age increased. Among men who drank alcohol in the last week (Fuller, 2015), 57% had consumed more than 4 units on at least one day and 29% had consumed more than 8 units in a day. Among women, 50% of those who had consumed alcohol in the last week exceeded 3 units on at least one day, and 22% had exceeded 6 units. It was unfortunate that these comparisons could not be shown for Wales and Northern Ireland due to lack of data. Mean weekly alcohol consumption statistics are not available for Wales, and estimates of consumption on the heaviest drinking day are not available for Northern Ireland (Government Statistical Service, 2014).

Similar to Scottish and British alcohol use disorder surveys, the majority of adults aged 15 years and over (n = 19,468) was low-risk drinking (64% of men and 90% of women) according to the Thai National Health Examination Survey V (Aekplakorn et al., 2015). The proportion of hazardous and harmful drinkers among Thai population was higher both men and women. Males aged group 25-34 years reported highest average AUDIT score, and 29% of this aged group had binge drinking behaviour which was also found in British surveys (Drummond et al., 2016).

Table 9-1 A comparison of AUDIT scores by country and gender

AUDIT scores classification	Thailand (2015)[a]	Scotland (2015)[b]	England (2016)[c]
Male			
Non-drinker/low risk (0-7)	64%	75%	72%
Hazardous drinking (8-15)	30%	21%	23%
Harmful drinking (16-19)	4%	2%	3%
Probable dependence (20+)	2%	2%	2%
Female			
Non-drinker/low risk (0-7)	90%	88%	85%
Hazardous drinking (8-15)	9%	10%	13%
Harmful drinking (16-19)	6%	1%	1%
Probable dependence (20+)	5%	1%	1%

[a] Aekplakorn, W., Pakchareon, H., Thaikla, K., & Sateannoppakao, W. (2015). Thai National Health Examination Survey V. Bangkok: Health System Research Institute.

[b] Gray, L., & Leyland, A. H. (2015). Chapter 4: Alcohol. In D. Campbell-Jack, S. Hinchliffe & L. Rutherford (Eds.), The Scottish Health Survey 2015 edition: Volumn 1 main report. Edinburgh: The Scottish Government.

[c] Drummond, C., McBride, O., Fear, N., & Fuller, E. (2016). Alcohol dependence. In S. McManus, P. Bebbington, R. Jenkins & T. Brugha (Eds.), Mental Health and Wellbeing in England: Adult Psychiatric Morbidity Survey 2014. Leeds: NHS Digital.

For alcohol-related death (Table 9-2), the Thai burden of disease reported 2,204 alcohol-related deaths for males and 310 deaths for females (Burden of Disease (BOD) and International Health Policy Program, 2014). To compare with alcohol-related deaths in the UK where the alcohol intervention model was developed, there were 8,697 alcohol-related deaths registered in the UK in 2014, equivalent to an age-standardised rate of 14.3 deaths per 100,000 population (Office for National Statistics, 2016). Of these, 5,687 deaths were among males (65% of the deaths) and 3,010 among females (35% of the deaths), with rates of 19.4 deaths per 100,000 males and 9.6 per 100,000 females. As presented in Table 9-2, Scotland had the highest age-standardised alcohol-related death rate for males at 31.2 deaths per 100,000 which it was likely similar figure in Thailand with rate of 28.2 deaths per 100,000 males. This

rate is significantly higher than those of any other constituent country of the UK; rates in Northern Ireland (20.3 per 100,000 males), Wales (19.9 per 100,000 males), and England (18.1 deaths per 100,000) were not statistically significantly different from each other. Moreover, Scotland also had the highest alcohol-related death rate for females at 13.3 deaths per 100,000 (Office for National Statistics, 2016). This rate is significantly higher than that in England, Northern Ireland and Thailand, but not different from that in Wales. Rates in Wales (10.4 deaths per 100,000), England (9.1 per 100,000), Northern Ireland (8.5 deaths per 100,000 females) and Thailand (8.7 deaths per 100,000 females) were not likely different from each other. Remarkably, deaths due to road traffic accidents in Thailand were substantially higher than in the UK with age-standardised death rates of 70.3 deaths per 100,000 males and 18.5 per 100,000 females for Thailand, but only 5.9 deaths per 100,000 males and 1.8 per 100,000 females for the UK (WHO, 2014).

Table 9-2 A comparison of alcohol-related death and age adjusted death rate by country and gender

	Male	Female
Alcohol-related deaths registered		
Thailand [a]	2,204	310
UK [b]	5,687	3,010
Age-standardised alcohol-related death rate per 100,000 males/females		
Thailand [a]	28.2	8.7
UK [b]	19.4	9.6
Scotland	31.2	13.3
Northern Ireland	20.3	8.5
Wales	19.9	10.4
England	18.1	9.1
Age-standardised death rate due to road traffic accidents [c]		
Thailand	70.3	18.5
UK	5.9	1.8

[a] Burden of disease (BOD) & International Health Policy Program (2014)

[b] Office for National Statistics, National Records of Scotland, Northern Ireland Statistics and Research Agency (2016)

[c] WHO. Global status report on alcohol and health (2014)

9.2 Conceptual framework of developing the Thai Health Promotion Intervention model for economic evaluation

To estimate the cost-effectiveness of a health promotion intervention, and particularly for this study which focussed on an alcohol intervention on different levels (e.g. individual and population), an economic evaluation alongside RCTs might be limited. As such, a combined approach would be needed to estimate the costs and outcomes of the alcohol intervention while avoiding biased estimates. Even though existing economic evaluations alongside RCTs were conducted to assess intervention cost-effectiveness (Cowell et al., 2012, Crawford et al., 2014, Crawford et al., 2015, UKATT Research Team, 2005a), these estimates were measured within the follow-up period and may not have captured the results of the alcohol intervention because they often become noticeable many years after implementation. Thus, the extrapolation of costs and outcomes beyond the end of the trial using observational data to link intermediate outcomes with final outcomes should be considered to extend the time horizon analysis (e.g. for the lifetime of different drinking patterns). This study will develop a health promotion intervention model that can evaluate the effectiveness and cost-effectiveness of interventions to inform health policy decision-making (Lewsey et al., 2015).

To account for the range of related risk factors that would likely affect hospitalisations and death, the development of the health promotion intervention model focussed on the association between related risk factors and harms (i.e. morbidity and mortality) to predict LYs and QALYs of different health risk profiles. These risk factors were identified to be the patterns and levels of alcohol consumption, socioeconomic status (Probst et al., 2015a, Jones et al., 2015b), as well as other factors which were found to have a relationship with alcohol drinking such as smoking status (Aekplakorn et al., 2008, De Leon et al., 2007, Falk et al., 2006, Harrison et al., 2008, McKee et al., 2010), physical activity (Kendzor et al., 2008), and body mass index or BMI (Hart et al., 2010). This study examines whether the selected risk factors are able to

accurately predict hospitalisations and death. Then, the model will be developed to estimate the LYs, QALYs, and lifetime healthcare costs, and those outcomes will be presented via different risk profiles. Moreover, the findings can be used for the evaluation of interventions that aim to change these selected risk factors, and it can show the association between the modified risk factors (intermediate outcome) and health outcomes.

To evaluate the effect of the alcohol intervention in the long-term using an intermediate outcome, a conceptual model of the relationship between biomarkers, surrogate endpoints, and the process of evaluating therapeutic interventions can be applied (Biomarkers Definitions Working Group, 2001, Buyse et al., 2010). The biomarker measurements (as compared to the risk behaviour in this study) can help explain the empirical results of clinical trials by investigating the relationship between the effects of interventions on molecular and cellular pathways and overall clinical responses. The biomarkers that represent highly–sensitive and specific indicators of disease pathways have been used as substitutes for the final outcomes in clinical trials when evidence indicates that they predict clinical risk or benefit. Figure 9-2 presents a conceptual framework of the development of the Thai Health Promotion Intervention model adapted from the Biomarkers Definitions Working Group 2001(Biomarkers Definitions Working Group, 2001, Buyse et al., 2010). A health promotion intervention can have direct and indirect effects on a wide range of an individual's modifiable risk factors, e.g. an alcohol consumption control intervention could change the alcohol drinking pattern and other related risk behaviours (e.g. cigarettes per day). Consequently, a mathematical analysis will examine that subset of risk factors, represented in the figure by a quadrant that can achieve surrogate endpoint status in terms of accuracy (correlation of measure) and precision (reproducibility); these are required to be reasonably likely to predict the endpoints in term of morbidity and mortality. Subsequently, the final outcomes can be converted to LYs, QALYs, and lifetime costs, and then the cost-effectiveness of the intervention can be estimated.

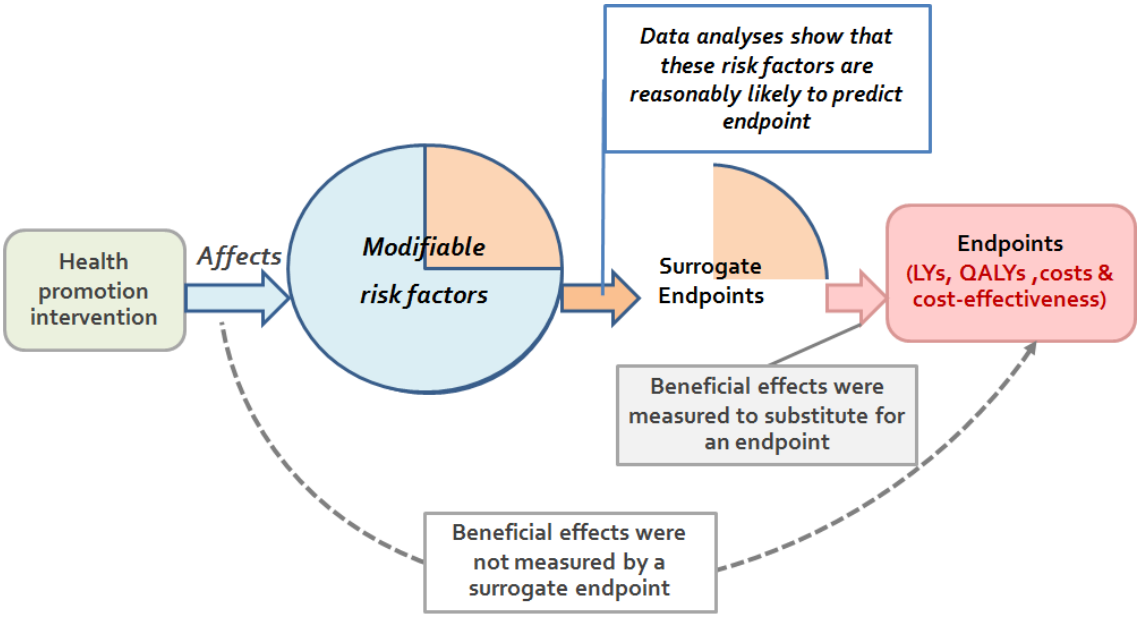


Figure 9-1 A conceptual framework of developing a health promotion intervention model for economic evaluation

*adapted from the (Biomarkers Definitions Working Group, 2001)

9.3 The objectives of study

1) To develop the Thai Health Promotion intervention model which can be used for the economic evaluation of health promotion interventions.

2) To demonstrate the usefulness of the Thai Health Promotion intervention model by conducting an economic evaluation of a selected existing alcohol intervention.

9.4 Methods

Based on the literature review about the effectiveness of interventions on reducing harm caused by alcohol consumption, a stakeholder consultation meeting will be conducted to discuss two main purposes as follows: 1) selecting an alcohol intervention of interest in the Thai context for economic evaluation which public health policy decision-makers would have an interest in, and 2) discussing the appropriateness of the approach used for the development of

Thai Health Promotion intervention model. To demonstrate the usefulness of the model, this study will apply a mathematical approach which was primarily developed to evaluate the alcohol intervention in the Scottish setting, namely the Scottish alcohol intervention model. The Scottish model was structured using a health state transition model to characterise the plausible consequences (i.e. hospitalisation and death) of different drinking behaviours (as detailed in Chapter 8: Section 8.2.1). The Scottish model was well-validated and calibrated, and is consistent with the key features of economic evaluation, such as perspective, time horizon, and measured costs and outcomes (Briggs et al., 2006c, Drummond MF et al., 1997, Gray et al., 2011a).

Then, the LYs, QALYs, and lifetime economic costs will be estimated from the Scottish alcohol intervention model, categorised by alcohol drinking patterns. These outcomes and costs of different drinking behaviours can be used to determine the benefits in terms of cost-effectiveness in the event that an alcohol intervention can change alcohol consumption, i.e. LY gained, QALY gained, lifetime economic costs and ICER. Therefore, the Scottish alcohol intervention model will be applied for developing the Thai Health Intervention model since the estimated outcomes and costs are suitable for health economic evaluation purposes. Additionally, these outcomes are widely recommended for the purposes of economic evaluation of health interventions, including recommendations from the Thai HTA guidelines to inform policy decision-making in the Thai context based on these outcomes (ISPOR, 2014, NICE, 2013, Chaikledkaew and Kittrongsiri, 2014, Teerawattananon and Chaikledkaew, 2008). Initially, The Thai Health Intervention model will introduce the model for the economic evaluations of alcohol interventions.

9.4.1 Estimating risk of hospitalisation and death among difference drinking pattern

To develop an analytical model for predicting LY, QALY, and lifetime costs, an extensive individual linked health data set between baseline risk behaviours measured from health surveys and administrative data set (i.e. hospitalisation and death record) after the survey date were required. In

Thailand, a linked dataset between national health surveys and national hospitalisation and death records is very scarce so this was an important limitation when developing the Thai Health Intervention model by using the same method as the Scottish model. The alternative used was to adapt the well-validated model using longitudinal data derived from other settings (Daniel Mullins et al., 2014, Stout et al., 2009);all data sets would be used to calibrate the cause-specific hazard model derived from the Scottish setting, and a multiplying factor would then be derived for adjusting the linear predictor of the original equation. Then, the calibrated model would be applied to estimate the risks of hospitalisation and death (as shown in Figure 2). There are four existing data sets that will be investigated using these alternatives as listed below:

1) The National Health Examination Survey V (2013) conducted by the National Health Examination Survey Office, where alcohol consumption and the Alcohol Use Disorder Identification Test (AUDIT) were collected.

2) The 2007 National Household Survey for Substance and Alcohol Use (N=26,633), which includes information on pattern of alcohol consumption, the AUDIT and consequences of drinking

3) The national survey of willingness to pay for selected health promotion programmes under ThaiHealth conducted by the Health Intervention Technology Assessment Program (HITAP) in 2012, which measured modifiable risk factors including alcohol consumption, smoking, physical activity, and socioeconomic status (N=7,311).

4) Baseline morbidity and mortality of alcohol-related condition reported by the Thai Burden of Diseases (BOD)

After data access requirements were approved, all researchers needed to correspond to the safe use of individual patient data with good practice methods and awareness patient data protection in order to analyse the administrative data. Thus, all researchers who accessed individual patient data

and produced the report were required to attend the Safe Researcher Training (http://www.adls.ac.uk/safe-researcher-training/) to have basic knowledge on how to treat administrative data in a responsible manner. Additionally, the study protocol was approved by the Institute for the Development of Human Research Protections (IHRP) as shown in Appendix 6.

9.4.2 Cost-utility analysis (CUA)

To estimate the cost-effectiveness of an intervention which aims to modify selected risk factors, two scenarios are performed for each individual risk profile. The first scenario model estimates the lifetime costs and health outcomes (i.e. LYs and QALYs) of the baseline risk profiles. The second scenario estimates these costs and outcomes of changes in risk behaviours (e.g. reduction of alcohol consumption) where the intervention affects these modifiable risk factors, leading to changes of first hospitalisation and death risks as well as healthcare costs and QALY. Next, the estimated lifetime hospitalisation costs and health outcomes are compared between the baseline and intervention effect scenarios, and incremental-cost effectiveness ratio (ICER) - that is, the additional cost per additional unit of effect (i.e. QALY) from a new intervention; thus, the ICER of a CUA is the incremental cost per QALY gained (Briggs et al., 2006c, Drummond MF et al., 1997, Gray et al., 2011b). Then, the ICER of the intervention will be compared to the threshold ICER of 160,000 THB per QALY gained as recommended by the Thai Subcommittee for Development of the National List of Essential Medicines (NLEM) and the Subcommittee of the Development of Benefit Package and Service System, National Health Security Office.

9.4.3 Input parameters

This stage describes the input parameters required for the model-based economic evaluation to estimate LYs, QALYs, and lifetime costs of the selected alcohol intervention; these parameters will be derived from expert consultation meeting. This analysis will estimate the costs and health outcomes of the two scenarios (providing the intervention and baseline). The base-case scenario will estimate the lifetime consequences of baseline risk behaviours (i.e. drinking

and related-behaviours) while the second scenario - the intervention - will compare the results in the changes of morbidity and mortality risks due to the intervention's effect on modifying risk behaviours (e.g. stopping drinking) to the baseline. This should lead to differences in the estimated lifetime costs and health outcomes compared to base-case.

Intervention effectiveness

To apply a recommended framework for evaluating the public health impact of health promotion interventions (Glasgow et al., 1999), namely the RE-AIM framework as described in Chapter 8. This study will explore the intervention's effect on alcohol consumption in the first year of implementation, duration of maintenance of intervention effectiveness, percent coverage rate, and acceptance rate in the Thai context. All effectiveness parameters will be verified by an alcohol expert panel. In addition, to generate QALYs, the baseline utility will be derived from the EQ-5D-5L measurement. The existing data were collected by the National Epidemiological Survey of Mental Health 2013-2014 (N~5,000) conducted by the Department of Mental Health, the Ministry of Public Health using Composite International Diagnostic Interview or CIDI, where alcohol abuse and alcohol dependence were diagnosed, as well as the EQ-5D-5L of respondents. The EQ-5D-5L measurement will be converted into a utility score using the Thai EQ-5D-5L preference (Pattanaphesaj and Thavorncharoensap, 2015).

The impact of hospitalisation will be estimated as utility decrements which will be collected from alcohol-related hospitalised patients. For non-alcohol related hospitalisation, the utility decrements of specific diseases will be derived from literature review using the Thai HTA research database (http://db.hitap.net/). The utility decrements will then be applied to decrease the baseline utility for the hospitalised health state. Moreover, the annual probabilities of re-admission will be estimated until the lifetime horizon. To calculate overall QALYs using the Kaplan-Meier Sample Average (KMSA) estimator approach (Gray et al., 2011a), the sum of survival time in each health

state weighted by the utility index adjusted by probabilities of re-admission and utility decrements will be calculated over 100-year cycle.

Intervention costs

The economic evaluation will be conducted from a societal perspective so lifetime costs will take into account direct medical care cost, direct non-medical care costs (i.e. transportation, meal, and accommodation related to medical care), and costs of productivity loss due to sick leave for hospitalised patients as well as costs of reduced productivity related to alcohol drinking (Thavorncharoensap et al., 2010). Estimating each cost parameter is described as follows:

1) Intervention costs will be collected, which consists of the cost of development and implementation in setting. Subsequently, the cost of full implementation to other settings should be estimated to reflect the real- world situation of the adopted intervention (Kruger et al., 2014).

2) Direct medical care costs due to hospitalisation will be obtained from the NHSO hospitalisation data from years 2001-2015 that covers around 70% of the Thai population. This administrative hospitalisation data set – which includes the diagnosis-related group (DRG) of each episode - will be used to model the average annual cost due to the 1-year cycle length of health state transition model. The modelling costs of yearly hospitalisation classified by the ICD-9 and ICD-10 will be estimated (Appendix 1). According to the plausible range and distribution of cost data, the generalised linear model (GLM) framework will be applied for modelling healthcare cost using the gamma family and log-link function (McCullagh and Nelder, 1989, Dobson and Barnett, 2008).

3) Direct non-medical costs related to treatment (i.e. transportation, meals, and accommodation related to medical care) will be estimated using the Thai standard cost list database (http://costingmenu.hitap.net/) and the amount of healthcare utilisation.

4) For alcohol drinkers without any hospitalisation, the costs of reduced productivity related to alcohol drinking will be applied (Thavorncharoensap et al., 2010). The costs will be assumed constant until the age of 60 years or until retirement.

The lifetime costs of the intervention will be affected by intervention effectiveness, leading to change in alcohol drinking behaviour and the risk of hospitalisation.

9.4.4 Discounting

As recommended by the Thai HTA guidelines to inform policy decision making in the Thai context (ISPOR, 2014, NICE, 2013, Chaikledkaew and Kittrongsiri, 2014, Teerawattananon and Chaikledkaew, 2008), the guideline decided to use a discounting rate at 3% annually for all costs and outcome since public health interventions usually show their effect over the long-term. Afterwards, the rate will change to 4% for cost and 1.5% for outcome in the 30th year and onwards (Permsuwan et al., 2014).

9.4.5 Uncertainty analysis

A probabilistic sensitivity analysis (PSA) will be conducted to assess the uncertainty surrounding input parameters of the analytical model that will be mostly derived from multivariate regression analyses, where these parameters are correlated with others (Briggs, 2000). Thus, the uncertainty analysis will be performed using a variance-covariance matrix of those parameters to show the covariance relationship. Afterwards, an applied approach, namely the Cholesky decomposition, can be employed to generate correlated draws of random parameters from the multivariate standard normal distribution (Briggs et al., 2006a). For the next stage, a Monte Carlo simulation performed in Microsoft Excel 2010 (Microsoft Corp., Redmond, WA) will be employed to generate 5,000 iterations to demonstrate a range of plausible lifetime costs, health outcomes (LYs and QALYs), and ICERs.

The result of the analysis will be plotted in a cost-effectiveness plane (Briggs et al., 2006b, Black, 1990), which shows the difference (intervention minus base case) in effectiveness (△E) per patient on the horizontal axis versus the difference in cost (△C) per patient on the vertical axis. The slope of the graph is equal to ICER =△C/△E. When the ICER simulations are compared to the cost-effectiveness (CE) threshold at 160,000 THB per QALY gained, the simulations which have a lower slope than the threshold line are considered to be cost-effective. Moreover, to summarise uncertainty by considering how many of the ICER simulations on the cost-effectiveness plane fall below and to the right of different thresholds, a cost-effectiveness acceptability curve (CEAC) will be illustrated (van Hout et al., 1994, Briggs et al., 2006b, Fenwick et al., 2001, Briggs, 2000). The results will be further analysed for a relationship between the different values of the threshold and the likelihood of being a cost-effective option compared between base case and the selected intervention using a net monetary benefit (NMB) framework. The NMB employs the cost-effectiveness decision rule (ICER< ceiling threshold referred as λ) by rearrangement as follows:

$$\frac{\Delta C}{\Delta E} < \lambda$$

$$\Delta E \times \lambda - \Delta C > 0$$

The intervention is considered cost-effective if its NMB is positive at any value of the ceiling threshold. Using the results of the Monte Carlo simulation (5,000 iterations), the NMB of each iteration of the intervention can be calculated and NMB compared to the base-case at the specific threshold, and the proportion of these iterations being cost-effective (NMB>0) can then be plotted on the CEAC.

9.5 Discussion

To conduct a model-based economic evaluation of a health promotion intervention to capture short- and long-term outcomes for various sub-

populations by different health profiles, the individual records of linkage data between the national health survey, morbidity, and mortality are needed. In Thailand, there is no such adequate linkage data similar to the one in Scotland because the Thai health surveys, morbidity, and mortality data are separately managed by different organisations (as detailed in Section 9.4.1); there is the lack of a process to link those data. As a result, the study conducted in the Thai context will transfer the decision modelling of the health promotion intervention developed in the Scottish setting using individual linkage data between the SHeS and Scottish morbidity and death records. The study will use the Scottish model structure and coefficient derived from multivariate regression models which carried out a wide range of model input parameters (e.g. transitional probabilities, hospitalisation costs and utility values).

However, the level of transferability of each parameter used needs to be considered as described in Chapter 2 (Barbieri et al., 2010). Additionally, an external validation of the applied model should be conducted to prove that the model structure and parameter used are adequate in the Thai context. According to the Thai expert consultation meeting on 26th November 2014 (Appendix 7), an expert suggested that the external validation of the alcohol-related harm prediction model should be conducted using a survey design to interview about the drinking status and the AUDIT as well as QALYs directly or comparing to an existing cohort in Thailand.

Due to the limitation of available linkage data, a model calibration of the Scottish model will be employed using the national health survey for comparing health profiles as well as individual hospitalisation and death records. These data will be used to separately calibrate the Scottish model to fit with the Thai baseline data. However, the Thai data have several limitations that need to be considered prior to further analyses. Firstly, the Scottish model is adjusted for the under-reporting of alcohol consumption among survey participants using alcohol sales data before conducting the multivariate regression analysis (as described in Chapter 6: Section 6.2.4). Nevertheless, under-reported alcohol drinking information among the Thai survey population is scarce; moreover, sufficient alcohol sales data in Thailand does not exist.

Thus, the Thai model will employ the same level of under-reporting alcohol consumption and relevant assumptions as the Scottish model. Secondly, the national hospitalisation and death records in Thailand seem to under-report alcohol-related conditions, e.g. accidents and injuries caused by alcohol drinking have been under-reporting due to drink-driving legislation, or it was not defined to be the primary diagnosis for the hospitalised patient because it is not covered by universal health coverage scheme.

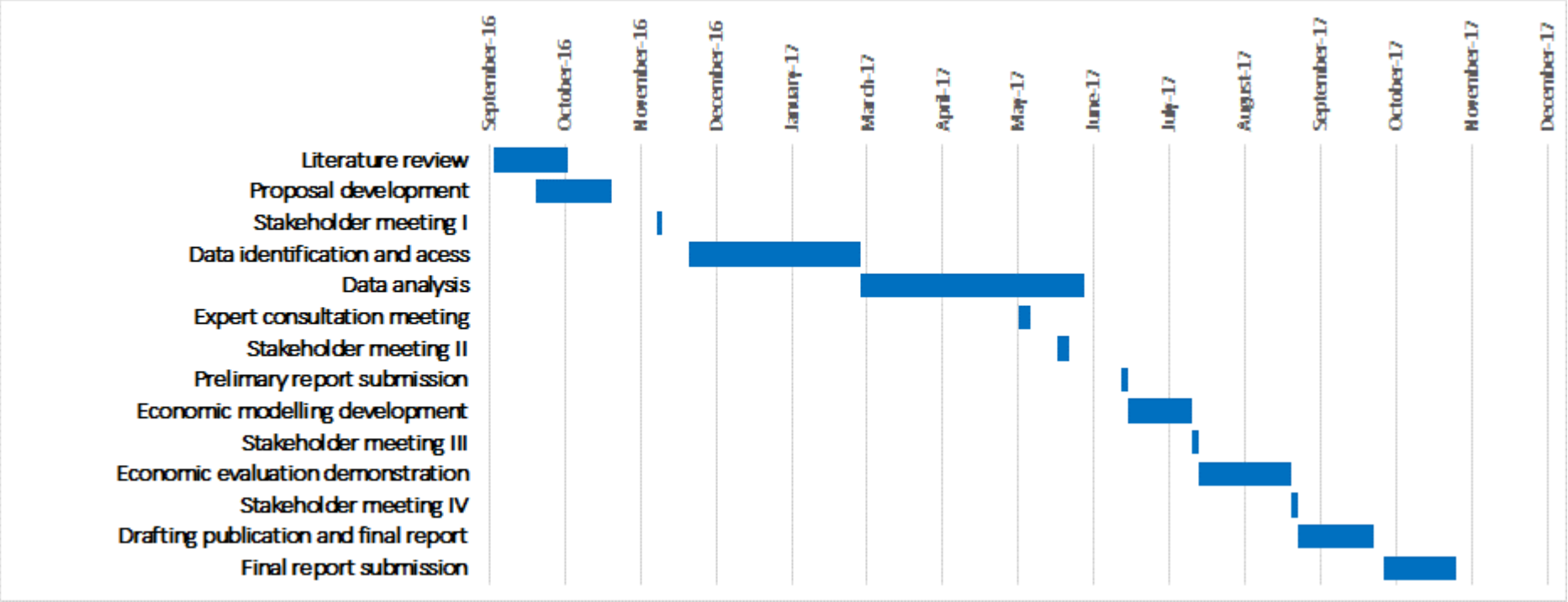
For utility and cost parameters, local data will be required due to the low level of transferability from other jurisdiction (Barbieri et al., 2010). There are two issues where the Thai study will be different from the original model. The first issue is due to the study using a societal perspective; as such the components of included costs are different from the Scottish study which used the healthcare provider perspective. The second issue is the HRQoL measurement, where the Scottish model estimated HRQoL using SF-6D (SF-12) HRQoL score (as described in Chapter 5). For the Thai study, EQ-5D-5L will be used based on recommendations by the Thai HTA guideline, and the Thai preference weights is also available (Chaikledkaew and Kittrongsiri, 2014, Pattanaphesaj and Thavorncharoensap, 2015). For these two parameters, the multivariate analysis should be re-analysed using country-specific dataset.

For intervention effectiveness, conducting an RCT in Thailand might not be suitable due to limited resources. Moreover, it might take a long time until the effects of the health promotion intervention become noticeable. Thus, this study prefers to combine relative risk estimates from international RCTs with the estimates of baseline risk from local epidemiological data (Barbieri et al., 2010). When data from more than one trial are available, a meta-analysis is the preferred method for synthesising clinical data. In particular, for one intervention that has been implemented only in Thailand, e.g. the annual “No alcohol during Buddhist Lent” campaign for a 3-month period, an observational study in the implemented setting will be used to estimate intervention effect while taking into account plausible confounders to reduce bias estimate.

9.6 Conclusions

This study will demonstrate an economic evaluation of an alcohol intervention in Thailand using the Thai Health Promotion intervention model, which will be developed via country-specific information. Therefore, this model will be suitable for the purpose of health promotion intervention evaluation to inform policy decision-making whether the intervention under evaluation is cost-effective in the Thai context. As a result, it is indeed fundamental, not only for justifying the public's investment in health promotion but also in enabling public health managers or healthcare workers to monitor the progress or success of their work. As mentioned above, economic evaluation for health promotion interventions in Thailand has been in high demand.

9.7 Study timeline



9.8 Budget estimation

Items	Cost per unit (THB)	Unit	Total cost (THB)
Staff			
Researcher (per month)	30,000	12	360,000
Research assistant (per month)	15,000	12	180,000
Research assistant (per month)	15,000	12	180,000
Materials			
Stakeholder meetings	20,000	4	80,000
International experts consultation meeting	100,000	2	200,000
Safe researcher training (per researcher)	5,000	3	15,000
Administration cost of data set	20,000	4	80,000
Statistic software	60,000	2	120,000
Office materials	50,000	1	50,000
Published report and policy brief	310	500	155,000
Publication	45,000	2	90,000
Financial statement audit	10,000	1	10,000
Total staff cost	720,000		
Total material cost	800,000		
Administrative cost (10% of material cost)	80,000		
Total	**1,600,000**		

Chapter 10: Discussion and conclusions

10.1 Introduction

The overall purpose of the thesis was to develop an alcohol intervention model that can be used to evaluate the long-term effectiveness and cost-effectiveness of alcohol interventions to inform health policy decision making. Moreover, the Thai public health and health promotion policy-makers are considering adopting the screening and treatment for alcohol use disorders so the alcohol intervention model will be useful for policy-making. The thesis explored the approaches used in previous alcohol intervention modelling and considered whether a new approach was need, and if so, what was an appropriate methodology to follow. Following gold-standard practices for developing an economic model, the current model required information as well as country-specific data, especially utility weight and cost data (NICE, 2013). Eight waves of a nationally-linked to morbidity and mortality data to develop cause-specific morbidity and mortality statistical models derived from individual risk factor profiles. Due to well-known under-reporting bias among the survey population, this study explored and demonstrated a potential approach to adjust under-reported alcohol consumption using alcohol sales data (Boniface and Shelton, 2013). Moreover, this study employed the Alcohol Use Disorder Identification Test (AUDIT), which has been widely used for screening and monitoring of alcohol use disorders – hazardous use, harmful use, and alcohol dependence - to examine the change of morbidity and mortality risks after modified alcohol use disorder (Babor et al., 2001).

Using a wide range of analytical methods for individual-level longitudinal data, the important components of the health state transition model for economic evaluation were estimated, i.e. time-dependent transitional probabilities of all possible events (alcohol-related and non-alcohol related diseases, and death), associated utility weight, and long-term healthcare costs related to hospitalisation and day cases. These input

parameters were used to estimate health outcomes (i.e. LYs and QALYs) and long-term healthcare costs classified by individual risk profiles e.g. age, sex, SIMD, and drinking risk. Then, the application of the alcohol intervention model was demonstrated for the economic evaluation of intervention that aims to change the selected risk factors. The results of cost-effectiveness could be detailed a large number of subgroups varied by such risk profiles. The additional proposal of methodological transferability to an LMIC country (i.e. Thailand) was included to plan for further study. This chapter discuss the overall thesis and provides a conclusion to the thesis. There are four parts that include a summary of main findings as well as a comparison with previous studies, strengths and limitations of the current alcohol intervention model, suggestions for improvement and speculating on future research, implications for policy-makers, and conclusions.

10.2 Summary of the thesis and main findings

10.2.1 Chapter 1

Chapter 1 introduced the background and overview information about the conceptual causal model of alcohol consumption and alcohol-related harm, and highlighted how alcohol-related harm is an increasing global public health problem. The harm caused by alcohol drinking impacts both at the individual- and society-levels. Accordingly, monitoring alcohol consumption per capita was described both at aggregate-level (i.e. alcohol sales) and individual-level through national health surveys which measure self-reported alcohol consumption. It is well recognised that self-reported alcohol consumption generally represents an underestimate of actual consumption (ranged from 40% to 60%) compared to per capita sales data due to the three main issues, namely sampling frame, non-response bias, and under-reporting bias. To measure alcohol misuse prevalence, and to evaluate the association of alcohol misuse with alcohol-related morbidity and mortality, this underestimation needed to be accounted for. A screening tool for alcohol use disorder, namely the AUDIT, was described in terms of the content and application in healthcare settings

and general population surveys. Consequently, effective and cost-effective alcohol interventions to reduce alcohol-related harms were listed and summarised the findings of literature. Since the current study was conducting using the framework of a model-based economic evaluation of public health interventions, methodological issues for evaluating cost-effectiveness using the modelling approach of public health intervention were summarised based on the published guidance. The guidelines addressed the various methodological challenges due to wider impacts and longer-term measured outcomes of public health intervention compared to the evaluation of healthcare intervention. Finally, the issue of transferability to other settings was addressed.

10.2.2 Chapter 2

This chapter reviewed the published literature of model-based economic evaluations of alcohol interventions to explore how the current study could fill the evidence gap. There are various methodological challenges related to developing an economic evaluation of alcohol intervention using modelling approaches to tackle a range of alcohol-related consequences and alcohol intervention effects. The review found the high levels of heterogeneity in terms of type of economic evaluation and model use, model structure, considering costs and consequences, and sensitivity analysis. Furthermore, the previous modelling studies encountered some limitations that the current study attempted to address by adding evidence in the following areas: limited adjustment for under-reporting consumption; multiple sources of evidence on a range of model parameters which may increase the degree of parameter uncertainty; limited essential country-specific data; a lack of longitudinal data at the individual level to model incidence of morbidity and mortality; a limited number of identified drinking states and related consequences; and a lack of consideration for equity or inequality. Accordingly, this study developed an alcohol intervention model to evaluate the costs, outcomes and cost-effectiveness of alcohol interventions by applying the QALY-framework to inform healthcare policy-makings (National Institute for Health and Care Excellence (NICE), 2012).

10.2.3 Chapter 3

Chapter 3 described the main purposes and conceptual framework of this study, which examined the impact of alcohol intervention on drinking problems, e.g. alcohol misuse and binge drinking (intermediate outcome) as measured by the AUDIT (Babor et al., 2001), and morbidity and mortality (final outcomes). These outcomes can then be converted to LYs, QALYs, and long-term costs, and intervention cost-effectiveness can subsequently be estimated. Since several analyses would be conducted to retrieve the fundamental inputs of the economic model, the stages of data analyses were then summarised in the form of an analytical framework. The Scottish linkage data between national health surveys, namely Scottish Health Surveys (SHeS), and Scottish morbidity records (SMR) as well as death records (National Record Scotland: NRS) were mainly used for the whole study (Information Services Division, Fleming et al., 2012); this demonstrated the use of country-specific administrative data to develop an economic evaluation for informing local policy-makers. Even though there are some published studies that conducted such linkage data analysis to explore alcohol consumption and its harms, these epidemiological studies have not demonstrated any economic evaluation of an alcohol intervention (Gray et al., 2013, Gorman et al., 2014, Fleming et al., 2012, Katikireddi et al., 2017). The current study performed an epidemiological model analysis and used the model outputs to develop an alcohol intervention model for economic evaluation. Then, a cohort Markov model to simulate multiple diseases including all possible hospitalisation and death over lifetime for estimating long-term costs and health outcomes was detailed. However, this study could not deal with the change of individual risk behaviours overtime, so the key assumption was the stability of health behaviours (i.e. alcohol drinking and related behaviours) over time with same age, where health behaviours classified by age can be derived from SHeS; this approach was also applied in other UK studies (Brennan et al., 2014b, Brennan et al., 2016). However, due to limited time and resources, the developed economic model could illustrate only a hypothetical intervention (as shown in Chapter 8) instead of an implemented alcohol intervention in the Scottish context.

10.2.4 Chapters 4 and 5

There were two initial analyses that were necessary for the developing alcohol intervention model. Firstly, the AUDIT would be used for the estimation of the outcomes but it was not measured in the early Scottish Health Survey waves. In Chapter 4, the initial analysis was done on nine alternative statistical methods for predicting AUDIT scores. The best-fitted model was able to generate the overall score (i.e. OLS regression model separated by gender), yet each AUDIT question could not be specifically predicted. Moreover, the observed AUDIT scores were derived from general population surveys which addressed that when using the AUDIT in the context of surveys, it would have the possibility of a false positive in the total score compared to using it in the healthcare setting (Knibbe et al., 2006). Although the OLS method could properly predict the scores, these scores for most of the SHeS study samples was an important assumption of the further analyses. The latest meta-analysis showed the significant difference between mortality risk of alcohol use disorder and non-alcohol use disorder (Roerecke and Rehm, 2013). Although there are a variety of alcohol misuse assessment tools, this study selected the widely used tool, i.e. AUDIT, to examine the association of alcohol use disorders and related health consequences. This is because the AUDIT has been widely recommended for detecting alcohol use disorder as identified by the WHO ICD-10 in the UK healthcare setting and many other countries with translation into their own languages as well (National Collaborating Centre for Mental Health, 2011, Dybek et al., 2006, Gache et al., 2005, Li et al., 2011). The AUDIT has also been applied for mass-screening and national health surveys for detecting prevalence of alcohol use disorder among the general population as a means of supporting national policy-makers, and Thailand will be the setting for a further study (Aalto et al., 2009, Knibbe et al., 2006, Assanangkornchai et al., 2010). Currently, public health and health promotion policy-makers in Thailand are considering adopting the screening and treatment programmes for alcohol use disorders, and they are monitoring the magnitude of alcohol use disorder among the Thai population using routine national health surveys. It could be seen that using AUDIT seems to be suitable for this current study which ultimately aimed

to inform these policy-makers - who are focussing on drinkers with alcohol use disorders rather than alcohol consumption volume in general.

The second initial analysis shown in Chapter 5 presented the estimation of HRQoL scores (i.e. utility value) using the SF-6D (SF-12) preferences-based index that was measured in only the SHeS 2003. The baseline HRQoL scores of the general population classified by age, sex, and SIMD quintile were estimated. In addition, a multivariate analysis was also performed to estimate the decrement of HRQoL or disutility score associated with different alcohol drinking statuses classified by the AUDIT score, and alcohol-related and non-alcohol related hospitalisations. Baseline HRQoL and disutility scores were used for the further analysis of estimating QALY as presented in Chapter 7. The relationship between drinking (measured by the AUDIT) and HRQoL supported the J-shaped morbidity curve as suggested in the previous studies, where those who have never consumed alcohol reported a worse HRQoL than low-risk drinkers, and higher-risk drinkers showed a worse HRQoL (Petrie et al., 2008, Saarni et al., 2008, Valencia-Martin et al., 2013, Van Dijk et al., 2004). For the reduction of HRQoL related to hospitalisations, having either alcohol-related hospitalisations or CVD-related conditions affected the current HRQoL (measured utility), at approximately the same utility values (around 0.65-0.70) found in previous studies (Currie et al., 2005, Dan et al., 2008). However, the HRQoL derived from survey populations may find that healthy people are more likely recruited in the health survey, and unhealthy people - especially heavy drinkers – may participate less, so they would be less likely to respond regardless of their alcohol drinking levels – an issue of selection and non-response biases (Meiklejohn et al., 2012).

10.2.5 Chapter 6

The alcohol intervention model was initially developed and presented in Chapter 6. The stages of developing the model started with constructing a health state transition model which included first- and following hospitalisations, and subsequently modelling various scenarios until death. A

parametric survival analysis using the SHeS-SMR/NRS linkage data separated by gender were listed as follows: stage 1 was the estimation of risk of having first events; stage 2 was the estimation of risk of having following hospitalisations and survival after hospitalisations; and stage 3 was estimating total life years. Individual risk profiles were used for each stage, i.e. age, SIMD, health conditions (DM and CVD), drinking status measured by predicted AUDIT scores, binge drinking and other selected behavioural risk factors (e.g. smoking, BMI, and physical activity). In conjunction with developing the analytical model, under-reporting alcohol consumption was adjusted using alcohol sales data and multiple imputation of missing data among survey population. After modelling, the model validation (i.e. internal validation) and calibration of the linear predictor using the Scottish life table were also employed.

Then, the model utilisation for predicting life years of different risk profiles were demonstrated and the results were presented classified by age, gender, SIMD, alcohol misuse (i.e. shown as the AUDIT and binge drinking), and other related behavioural risk factors (e.g. smoking, BMI, and physical activity). The results showed that the developed alcohol intervention model could predict the hospitalisation and death events of each individual risk profile, and the model validation showed good performance. However, the predicted overall survival of different risks profiles was likely longer than the life table of the population so the linear predictor was adjusted with a multiplying factor generated from the Scottish life table (National Records of Scotland, 2014). Finally, predicting the overall LYs of different drinking statuses were demonstrated the use of the alcohol intervention model in evaluating the effect of alcohol intervention on morbidity and mortality. According to the method used as mentioned above, the current alcohol intervention model differed from other modelling studies so it would be difficult to directly compare with other alcohol intervention evaluation studies. The current study would be an alternative approach to develop a model-based economic evaluation. Where the previous modelling studies commonly gathered the model parameters from various sources, this study used national administrative data to generate the

various components of the analytical model. This can be a new area for linked health data analysis, of which almost all of previous studies focussed on dealing with survey population bias (i.e. non-response bias), assessing the representativeness of study population, and epidemiology of alcohol-related harm (Gray et al., 2013, Gorman et al., 2014, Katikireddi et al., 2017).

10.2.6 Chapter 7

Chapter 7 illustrated the use of the alcohol intervention model to estimate QALYs and long-term healthcare costs (i.e. hospitalised admission and day case) over the lifetime, and the results were comparable across risk behaviours (e.g. drinking status, smoking, physical activity, and BMI), subgroups by age, gender, and socioeconomic status. The results indicated how future healthcare costs and outcomes would change based on either an increase or decrease in alcohol use (measured by the AUDIT). To model the occurring plausible events in the long-term, the annual risk of subsequent hospitalisations for individuals who survived after first hospitalisations classified as alcohol-related and non-alcohol related conditions were estimated since these following events had effects on both the reduction of HRQoL and future treatment costs.

For estimating QALYs, baseline HRQoL values (categorised by age, gender, and SIMD) and the reduction of HRQoL values due to hospitalisations and increasing AUDIT scores (derived from initial analysis in Chapter 5) were multiplied by the annual risk of subsequent hospitalisations and weighted by LYs (as mentioned in Chapter 6). Finally, the sum of quality-adjusted survival of each annual cycle in different health states was calculated over the lifetime, and were presented as the remaining QALYs after entering the cohort model; the results showed the differences of the remaining QALYs compared across risk profiles. For each drinking risk categorised by the AUDIT score band, the results revealed that higher-risk drinking resulted in less remaining QALYs when other related risk profiles were also changed based on the characteristics of the study population. The estimated QALYs from this study may not be directly

comparable to other studies because of the differences in modelling methods, utility measurement, and defined drinking status; however, there is an only one UK study where the QALYs of harmful drinking (defined as grams of alcohol consumption per day) may be compared with the QALYs of this study (Barbosa et al., 2010a). Discounted QALYs derived from the UK study was 12.98 years (male cohort aged 40 years with harmful drinking defined as alcohol consumption ≥80 g/day) while discounted QALYs of the current model was 16.36 years for male aged 40 years with an AUDIT score of 16-19, i.e. harmful drinking. The approximately three-year difference between the two studies may be due to the difference in the utility measurement tool; the previous study obtained its utility value from the EQ-5D while this study used the SF-12 (SF-6D). Moreover, Barbosa et.al. applied a discounting rate of 3.5% per year following previous NICE recommendations (National Institute for Clinical Excellence (NICE), 2004), whereas this study followed a later recommendation specific to public health interventions and utilised a discounting rate of 1.5% per year (National Institute for Health and Care Excellence (NICE), 2012).

For estimating long-term costs using the healthcare perspective, this analysis used the SMR01 morbidity records which includes acute inpatient and day cases, and the health service costs of each episode was identified as alcohol-related and non-alcohol related condition. The annual costs in the year of having first hospitalisation and subsequent admissions in following years were then estimated using per diem costing; moreover, based on the previous study, fitting GLM was applied for predicting long-term costs (Jones et al., 2015a, Geue et al., 2012, Dodd et al., 2006). Nevertheless, the total long-term healthcare costs of the study population were not estimated due to a lack of diagnoses with ICD-9/ICD-10 for patients in the A&E department, outpatient, and primary care setting. Thus, the estimated costs will be useful only for comparison across risk profiles of the study population. The methods of measurement and valuation of relevant costs and included diseases in this study were difficult to compare with other settings so the comparison cannot be made for this discussion. This study analysed the Scottish linkage data as well as

applied Scottish health services costs. The results of this study could be specifically applied to the Scottish context with good internal validity, whereas the results may be lack external validity. However, the use of model adaptation can be applied to make this policy model more transferable to other settings (Daniel Mullins et al., 2014, Stout et al., 2009).

10.2.7 Chapter 8

Chapter 8 showed how the alcohol intervention model applies the economic evaluation of an intervention which aims to change the selected risk factors. The intervention was assumed that it would be able to stop drinking (measured baseline alcohol consumption by the AUDIT) and smoking (measured baseline by the number of cigarette per day) in all selected subgroups (best scenario), whereas other selected risk factors (e.g. SIMD, physical activity, and BMI) were assumed to be the same as baseline. Heterogeneity in patient characteristics were explored using a series of separate scenarios. These scenarios are explored by varying the mortality and morbidity rates according to the characteristics considered. The impact of the intervention on changing LYs, QALYs, and long-term hospitalisation costs were illustrated. Then, the full economic evaluation using a cost-utility analysis to compare between the base case and hypothetical intervention was conducted. Comparing the costs and benefits of the intervention and baseline over the lifetime period, a within-trial analysis combined with the developed model can capture both short- and longer- term consequences. For a further cost-effectiveness analysis of other health promotion interventions, this study demonstrated the structure of analysis model and specified the input parameter needed. Finally, the cost-effectiveness results were presented using a probabilistic model that took into account input parameter uncertainty, and the results were compared to the cost-effective threshold of the UK. Moreover, the cost-effectiveness results were classified into subgroups based on age, gender and different risk profiles; this would be used to inform the policy-making process and define target groups for interventions based on cost-effectiveness results.

10.2.8 Chapter 9

Finally, the protocol of methodological transferability study in Thailand and potential problems surrounding transferability to the Thai context were addressed. The Thai study's framework was developed to evaluate the alcohol intervention implemented in Thailand. The method used was developed and validated in the Scottish setting, and consisted of an alcohol intervention mathematic model for predicting LYs, QALYs, lifetime healthcare costs, and cost-effectiveness analysis.

10.3 Strengths and limitations

10.3.1 Strengths

The major strengths of this thesis are detailed in the numbered sections below.

1. *High quality data sources:* The model development has exploited the high-quality routine health data sets of Scotland known as the linkage data of SHeS-SMR/NRS; this study has developed a model-based economic evaluation after creating a nationally-representative cohort study following people up from survey participation for a maximum of 19 years (from 1995 to the end of 2013); very large cohort sample size (n = 46,230) as well as numbers of events (the total numbers of first alcohol related events = 1,150 cases and non-alcohol related events = 21,051 events).

2. *High internal validity:* The alcohol intervention model classified by individual risk profile is extremely data-demanding and needs country-specific data such as annual risk of morbidity and mortality - which varied by strata formed by the variables of age, gender, socioeconomic status, alcohol drinking, and other behaviours. Such variable often cluster or co-occur with drinking such as smoking and physical activity and this model has captured such co-variation and is built into the economic model. Moreover, alcohol intervention effectiveness and cost data, cost data for alcohol-related conditions, and utility

weights for health state transition model were required. These input parameters were derived from the single source longitudinal data at the individual level, which produces high internal validity. The same data sources (from Scotland) were used for developing all the components of the decision analytic model (e.g. baseline risk classified by risk profiles, morbidity and mortality incidence data over time, health related quality of life, and healthcare costs). When compared to other existing alcohol intervention models, those studies employed evidence synthesis to generate transitional probability and relative risk of morbidity and mortality of higher risk drinking.

3. *New high-quality evidence on association between AUDIT and health outcomes:* There is scarce evidence that reveals the association between the measured AUDIT score and alcohol-related consequences (e.g. mortality and morbidity). This study explored the association of measured AUDIT scores in survey population and alcohol-related diseases and death. Nowadays, the validated AUDIT is recommended for alcohol use disorder screening and treatment in the primary healthcare setting in the UK, and has been translated into other languages in many other countries including Thailand. It can evaluate the effects of treatment by measuring the impact of treatment on general alcohol problems using self-completed questionnaires. Thus, the use of predicted AUDIT scores for modelling can extrapolate the health impact caused by alcohol use disorder which is generally defined as the same ICD-10 across countries. This will be an advantage as the current model can be adapted to other jurisdictions where the AUDIT is applied in their healthcare settings and general population surveys for estimating alcohol use disorder prevalence.

4. *Incidence-based model:* Several alcohol models exist. In particular, the Sheffield model is the most well-known in the UK and focusses on the expected disease prevalence for various population cohorts (prevalence-based approach) related to alcohol consumption. As such, this needs to deal with time lag effects for chronic conditions where the development of a disease often occurs over many years. While the Sheffield model assumed the time lag of obtaining the full benefits associated with a reduction of consumption based on the best

available evidence, this study used incidence-based approaches to estimate time-dependent risk of hospitalisations and deaths due to such chronic conditions for individual risk profile including alcohol consumption.

5. *Broad modelling scope:* More possible health states of study cohort were modelled using the health state transition model of a single individual cohort, and the transitional probability of each heath state was estimated from parametric survival models to extrapolate health-related consequences over a lifetime horizon. This study applied the AUDIT for the outcome measurement of the alcohol intervention because the AUDIT can capture a wider range of alcohol drinking problems based on 0 to 40 scores so the subgroup analysis could be performed as classified by the scores. Moreover, this study was concerned about the under-reporting bias of alcohol consumption; therefore, the level of alcohol consumption among the survey population used for predicting AUDIT scores and identifying binge drinking was adjusted by using alcohol sales data.

6. Strong comparability between model development and initial model use settings: This study aims not only to develop an alcohol intervention economic model but also to transfer the approach used to an LMIC setting (Thailand). This thesis showed strong comparability between two settings in terms of the magnitude of alcohol consumption and its related-problems – which Scotland and Thailand were found similar figures of alcohol use disorder problem and alcohol-related death rate among men. Thus, this model has been potentially transferred to Thailand as well as the framework of future study in Thailand has been detailed.

10.3.2 Limitations

1. From the health state transition model (shown as Figure 3-3), the change of service provision for disease screening and other primary care services would not affect the analysis since only hospitalisations were included. However, if service provision related to hospitalisation was improved such as reducing the waiting time for cancer treatment, the probability of hospitalisation due to

such conditions would increase. Thus, this analysis was based on the service deliveries at the time period of the occurring event only.

2. There were time and resource constraints within this study which did not allow for a societal perspective to be analysed. Moreover, some costs and outcomes might be difficult to capture due to limited resources for primary research within this area. Non-health consequences were not included i.e. socioeconomic consequences (loss of earnings, unemployment, homelessness, poverty, family disruption, and stigmatisation) (WHO, 2004, Schmidt et al., 2010). Harm to other individuals (e.g. spouse or partner, child, co-worker, case of traffic crashes and violence) was also not included, e.g. death or a lifelong disability for accident victims.

3. Over half (53% for males and 51% for females) of the SHeS participants who had no prior alcohol-related hospitalisation were alive and did not yet experience one of the first events. In addition, over 85% of those who experienced first hospitalisation after the survey date were still alive. These might result in potential survey bias and limited duration of follow up, especially for most recent survey year as described below:

3.1) Selection bias and non-response bias of the SHeS since healthy people are more likely to be recruited in the health survey. At the same time, if unhealthy heavy drinkers were recruited, they would be less likely to respond regardless of their alcohol drinking levels. As a result, the probability that this study lacks data from unhealthy people would be high, which would underestimate the effect of high-risk drinking on health.

3.2) The SHeS-SMR/NRS linkage data was limited to hospitalisation and death in hospital events (i.e. SMR01), so it would likely underestimate the risk of diseases which will occur in a primary care setting, non-hospitalised conditions, and death due to road traffic accident. The follow-up time of later SHeS (e.g. survey year 2010-2012) would be too short for developing chronic diseases (e.g.

CVD and cancers), so these conditions might not present in hospitalisation records and especially death from the conditions.

These would likely affect the long tail survival curves without any model calibration. Although the parametric survival models were shown to be highly statistically significant, these models can be updated to re-predict life expectancy using updated linkage data (see section 10.4). Furthermore, for health economics analysis, the estimated outcomes and healthcare costs, especially an expensive condition such as cancer will not yet have captured in the linkage data, and this is likely underestimate cost effectiveness results of an alcohol intervention.

4. HRQoL status might vary among individuals with the same health status since other variables related to health status were not taken into account. This analysis adjusted for some confounders which were available, but possibly not all because data was not available; some may not have been measured or recorded while some were unknown confounders.

5. The use of the predicted overall AUDIT score for almost all of the SHeS data sets (7 of 8 survey years) is an important assumption in predicting outcomes (i.e. hospitalisation and death). The overall AUDIT was predicted using self-reporting long term health condition (having CVD), and the following analysis as cause-specific hazard model of first CVD hospitalisation was also included the predicted AUDIT. This is leading to a lack of independence between AUDIT and the first CVD hospitalisation. Although the results showed that there were no statistically significant increasing risks of having first CVD hospitalisation for a unit increase in the predicted AUDIT score, care should be taken when interpreting the relationships between the predicted AUDIT score and outcomes of interest due to its limitation.

6. There were no longitudinal risk behaviour profiles of the survey study population, whereas the developed model focussed on the relationship between the selected modifiable risk factor and the risk of first events (i.e.

hospitalisations and deaths) without information about risk behaviours on the date of having first event. Thus, the model would be applied only for the evaluation of a primary intervention which aims to reduce the risk of the first event of interest under the assumption that the respondent who has the first event will not change his/her risk behaviours from the survey date. Moreover, socioeconomic deprivation is measured by the Scottish Index of Multiple Deprivation (SIMD). This was classed as non-modifiable risk factor so the study population assumed the same status over time. In addition, the SIMD quintile was selected to be the measurement of socioeconomic status of this analysis to investigate health inequality among study population, so the index cannot apply for other settings. However, the linear predictor of the model can be recalibrated using country-specific life tables and SIMD quintiles as a covariate that can be replaced with other deprivation indices.

10.4 Areas for further research

The key areas for future research are listed below, in order of priority.

1. The current study focussed on alcohol use disorder and its impact on individual hospitalisations, deaths and lifetime hospitalisation costs. It is possible that intervention may reduce A&E incidence and primary care consultations, and increase admission or vice versa. Further studies should explore a more comprehensive linkage beyond inpatient data. Therefore, the total healthcare costs and other health conditions should be estimated using alternative longitudinal data e.g. SHeS linked to SMR00 (outpatient attendance) and Accident and Emergency when they are completely linked to the SHeS record and diagnoses are identified for all individual patient. Moreover, the Prescribing Information System (PIS) would be explored; PIS includes prescribing, dispensing and reimbursed data by a range of healthcare practitioners including GPs, nurses, dentists, pharmacists and an expanding range of other non-medical prescribers (Alvarez-Madrazo et al., 2016). PIS has been connected to further datasets by using electronic record linkage e.g. SMR00 and SMR01. Therefore, the resource use (i.e. prescribed medicines) in

primary care setting would be possible to include in estimating healthcare costs. Currently, in Scotland, the linkage of primary care records is ongoing work, namely the SPIRE project (http://spire.scot/), so the use of general practitioners (GPs) patient records is possible for use in the future study. For example, it would provide repeated measurement on individual behaviours such as alcohol drinking, smoking, and BMI. In the UK, the CPRD is currently the best way forward for linking primary and secondary care records (https://www.cprd.com/intro.asp).

2. There will be an opportunity to acquire updated SHeS-SMR/NRS linkage data (i.e. 2013 onward) where the AUDIT has already included in the survey, and the current study population will have a longer follow-up period as well as new cohorts. This updated data can then be used to re-analyse the following: 1) the analysis of predictive performance of all predicting AUDIT score models to test whether OLS regression will obtain the best predictive model; and 2) the modelling risk of events derived from recent linkage data where more event of interest will have been observed. These analyses can provide an opportunity to re-estimate models with higher statistical power.

3. The societal perspective has been recommended for the economic evaluation of public health and health promotion intervention because of its wider perspective (Weatherly et al., 2009, Lorgelly et al., 2010, Chalkidou et al., 2008). Further research should be conducted to account for the wider impacts of alcohol consumption on the whole society such as productivity loss due to sick leave or blackout from high-risk drinking, harms to others, and crime and violence. widening linkage beyond healthcare data. It is also possible that the future research will use the increasing types of linkage data beyond healthcare, e.g. link to work and pensions data and criminal records.

4. An important issue for further research is a health outcome measurement of alcohol drinking control intervention; therefore, these studies should prospectively investigate the change of HRQoL along with the AUDIT over time. Moreover, these studies should consider the measurements for alcohol use and

HRQoL since they should be able to capture the effect of alcohol consumption on HRQoL unless it is found that the reduction of alcohol drinking risk does not show any significant improvement in HRQoL (Essex et al., 2014, UKATT Research Team, 2005b).

5. Alcohol related harm is an important public health issue worldwide. This issues also seems to relate to specific cultures and inequalities in health. This model could classify the effect of alcohol intervention by socioeconomic status, so adapting this model to different countries would be valuable e.g. research in LMIC. Since socioeconomic status (as measured by the SIMD) is a key factor of the current alcohol intervention model, it can reflect the inequality in health that has been the focus of public health policy. Hence, future studies in other countries should define the standard tool for measuring socioeconomic status in their context and apply the measurement across the same geographical area (e.g. country level); the measured socioeconomic status should be a key covariate of a further alcohol intervention model in the future alcohol intervention model.

6. The model was constructed to evaluate the effectiveness and cost-effectiveness of an intervention which aimed to change individual risk profile as demonstrated. However, it would be interesting to apply the model for an evaluation of a public health intervention which aims to shift the distribution of population risk (e.g. population-level intervention). Other modelling approaches such as system dynamics, discrete event simulation describe the interactions of heterogeneous individuals with their environment. There is therefore a need to justify the model structures which are developed and the level of complexity employed (Squires et al., 2016).

10.5 Implications for policy-makers

The information is useful for policy-makers who are focussing on alcohol interventions which aim to reduce harms caused by alcohol consumption; moreover, the results derived from model could classify a large number of subgroups varied by heterogeneity characteristic of population, so this could be used to help policy-makers in targeting groups of such intervention based on cost-effectiveness results. In addition, the results derived from the alcohol intervention model using the Scottish linkage data can be specifically applied to the Scottish context with good internal validity. This can demonstrate usefulness of collecting and linking routine data, i.e. national health surveys and national healthcare administrative data, and such data can be applied for generating a wide range of health research to inform the policy-making process. Public health policy-makers may be interested in widening their perspectives apart from the health sector so the linkage for routine non-health data (e.g. crime records and employment data) should be improved for capturing a broader impact of alcohol intervention. Moreover, the protocol for future studies in other settings was detailed to guide local researchers who will transfer this method and conduct an economic evaluation of an alcohol intervention to inform their local public health policy-makers.

10.6 Conclusions

The study highlights the potential and importance of developing health economic models utilising data from routine national health surveys linked to national hospitalisation and death records. The developed framework can be used for further economic evaluation of alcohol interventions and other health behaviour change interventions. The framework can further be transferred to other country settings.

Appendix 1

Alcohol conditions and International Classification of Diseases (ICD-9 and -10) codes

	ICD-9 codes	ICD-10 codes
Wholly attributable conditions		
Mental and behavioural disorders due to use of alcohol	291, 303, 305	F10
Degeneration of nervous system due to alcohol		G31.2
Alcoholic polyneuropathy	357.5	G62.1
Alcoholic myopathy		G72.1
Alcoholic cardiomyopathy	425.5	I42.6
Alcoholic gastritis	535.3	K29.2
Chronic (incl.) alcoholic liver disease	571.0-571.5, 571.8, 571.9	K70 K73, K74.0-K74.2, K74.6
Alcohol-induced chronic pancreatitis	577.1	K86.0
Excessive blood level of alcohol	790.3	R78.0
Toxic effect of alcohol (Ethanol&Metanol poisoning)	980	T51.0, T51.1, T51.9
Accidental or intentional poisoning by and exposure to alcohol	E860.0, E860.9	X45 X65
Poisoning by and exposure to alcohol, undetermined intent	9805	Y15
Evidence of alcohol involvement determined by blood alcohol level		Y90
Evidence of alcohol involvement determined by level intoxication		Y91
Alcohol-induced acute pancreatitis (2014)	577	K85.2
Alcohol rehabilitation (excluded 2014)	V57	Z50.2
Alcohol deterrents (excluded 2014)	E947.3	Y57.3
Alcohol abuse counselling and surveillance (excluded 2014)		Z71.4
Alcohol use (excluded 2014)		Z72.1
Partly attributable-chronic conditions		
Malignant neoplasm of lip, oral cavity and pharynx	140,141-146,148-149	C00-C14
Malignant neoplasm of oesophagus	150,151	C15
Malignant neoplasm of colon	153	C18, C19, C21
Malignant neoplasm of rectum	154	C20
Malignant neoplasm of liver and intrahepatic bile ducts	155	C22
Malignant neoplasm of larynx	161	C32
Malignant neoplasm of breast	174	C50
Diabetes mellitus (type II)	250	E11
Epilepsy and Status epilepticus	345	G40-G41
Hypertensive diseases	401-405	I10-I15
Ischaemic heart disease	410-414	I20-I25
Cardiac arrhythmias	427.0,427.2,427.3	I47-I48
Haemorrhagic stroke	430-438	I60-I62, I69.0-I69.2
Ischaemic stroke		I63-I66, I69.3-I69.4
	ICD-9 codes	**ICD-10 codes**
Partly attributable-chronic conditions (cont.)		

Oesophageal varices	456.0-456.2	I85
Unspecified liver disease	571.5-571.9	K73, K74
Cholelithiasis	574	K80
Acute and chronic pancreatitis	577, 577.1	K85, K86.1
Spontaneous abortion	634, 656.5	O03
Tuberculosis	10-18	A15-A19
Pneumonia	480.8, 481, 482.41, 482.8, 484, 486, 487	J10,J11,J12-15, J18
Partly attributable-acute consequences		
Road/ Pedestrian traffic accidents	E810-E819, E826,E829	§
Fall injuries	E880-E888	W00-W19
Other unintentional injuries	E980-E989	§§
Drowning	E910	W65-W74
Fire injuries	E890-E899	X00-X09
Intentional self-harm/Event of undetermined intent	E950-E959	X60-X84, Y10-Y34,Y87,Y87.2
Poisoning	X40-X49	E860-E869, V15.6
Assault	E960,E965,E966,E968,E969	X85-Y09, Y87.1

§ = V021-V029, V031-V039, V041-V049, V092, V093, V123-V129, V133-V139, V143-V149, V194-V196, V203-V209, V213-V219, V223-V229, V233-V239, V243-V249, V253-V259, V263-V269, V273-V279, V283-V289, V294-V299, V304-V309, V314-V319, V324-V329,V334-V339, V344-V349, V354-V359, V364-V369, V374-V379, V384-V389, V394-V399, V404-V409, V414-V419, V424-V429, V434-V439, V444-V449, V454-V459, V464-V469, V474-V479, V484-V489, V494-V499, V504-V509, V514-V519, V524-V529, V534-V539,V544-V549, V554-V559, V564-V569, V574-V579, V584-V589, V594-V599, V604-V609, V614-V619, V624-V629, V634-V639, V644-V649, V654-V659, V664-V669, V674-V679, V684-V689, V694-V699, V704-V709, V714-V719, V724-V729, V734-V739, V744-V749,V754-V759, V764-V769, V774-V779, V784-V789, V794-V799, V803-V805, V811, V821, V830-V833, V840-V843, V850-V853, V860-V863, V870-V878, V892

§§ = V01, V090, V091, V099, V100-V109, V110-V119, V120-122, V130-132, V140-V142, V150-V159, V160-V169,V170-V179, V180-V189, V191-V193, V20-V28: 0.1-0.2; V290-V293, V30-V38: 0.1-0.2; V390-V393, V40-V48: 0.1-0.2; V490-V493, V50-V58: 0.1-0.2; V590-V593, V60-V68: 0.1-0.2; V690-V693, V70-V78: 0.1-0.2; V790-V793, V800, V801, V806-V809, V810, V812-V819,V820, V822-V829, V834-V839, V844-V849, V854-V859, V864-V869, V879, V88, V890, V891, V893-V899, V90-V94, V95-V97, V98-V99, W20-W52, W75-W84, W85-W99, X10-X19, X20-X29, X30-X33, X50-X57, X58, X59, Y40-Y84 Y85, Y86, Y88, Y89

Source:

1. Jones L, Bellis MA. Updating England-Specific Alcohol-Attributable Fractions. Liverpool: Centre for Public Health, Liverpool John Moores University 2013.

2. Jones L, Bellis MA, Dedman D, Sumnall H, Tocque K. Alcohol-Attributable Fractions for England. Liverpool: Centre for Public Health, Liverpool John Moores Universitythe and North West Public Health Observatory 2008.

3. Grant I, Springbett A, Graham L. Alcohol attributable mortality and morbidity: alcohol population attributable fractions for Scotland. Edinburgh: Information Services Division, NHS National Services Scotland 2009.

Cardiovascular disease International Classification of Diseases (ICD-9 and -10) codes (Excluded CVD attributable to alcohol consumption)

	ICD-9 codes	ICD-10 codes
Cardiovascular diseases	390-409, 415-429, 440-459	I10-I19, I26-I59, I70-I74

Appendix 2

Search terms for the methodological review

Search terms used in NHS EED (search conducted on the 18/12/2016**):**
1 MeSH DESCRIPTOR Alcohol-Related Disorders EXPLODE 1 2
2 MeSH DESCRIPTOR alcohol drinking EXPLODE 1
3 "alcohol drinking"
4 alcoholism
5 "alcohol consumption"
6 drink* NEAR excess*
7 drink* NEAR binge
8 drink* NEAR heavy
9 drink* NEAR hazard*
10 drink* NEAR problem*
11 drink* NEAR abuse
12 drink* NEAR misus*
13 drink* NEAR dependen*
14 drink* NEAR harm*
15 alcohol* NEAR excess*
16 alcohol* NEAR binge
17 alcohol* NEAR heavy
18 alcohol* NEAR hazard*
19 alcohol* NEAR problem*
20 alcohol* NEAR abuse
21 alcohol* NEAR misus*
22 alcohol* NEAR dependen*
23 alcohol* NEAR harm*
24 "alcohol intake"
#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
NHS EED = 188
Hand searching 2

Search term used in Ovid MEDLINE(R) <1946 to December Week 1 2016>
Search conducted 30/12/2016
1 exp "Costs and Cost Analysis"/ (221402)
2 "Value of Life"/ (6038)
3 Economics/ (9758)
4 Economics, Nursing/ or Economics, Medical/ or exp Economics, Hospital/ or Economics, Pharmaceutical/ (40151)
5 or/1-4 (276274)
6 (econom$ or cost$ or pric$ or pharmacoeconomic$).ti,ab. (611907)
7 (expenditure$ not energy).ti,ab. (22252)
8 (value adj1 money).ti,ab. (29)
9 budget$.ti,ab. (21156)
10 or/6-9 (634121)
11 5 or 10 (758489)
12 letter.pt. (962103)
13 editorial.pt. (424974)
14 historical article.pt. (512545)
15 12 or 13 or 14 (1875501)
16 11 not 15 (721901)
17 Animals/ (6734766)
18 Humans/ (18009599)

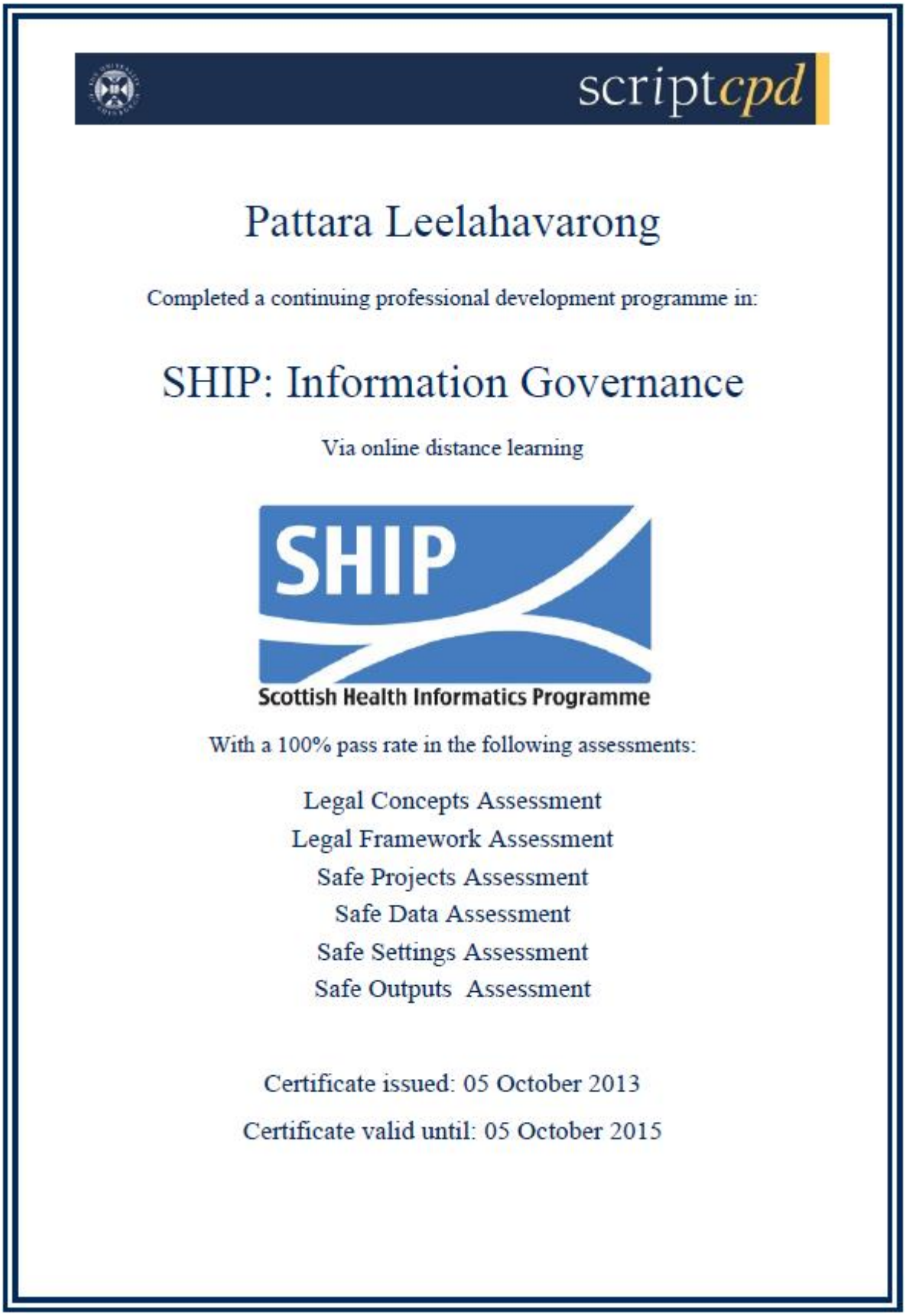
19 17 not (17 and 18) (4782110)
20 16 not 19 (662455)
21 (metabolic adj cost).ti,ab. (1053)
22 ((energy or oxygen) adj cost).ti,ab. (3212)
23 20 not (21 or 22) (659154)
24 *Alcohol Drinking/ (41229)
25 exp Alcohol-Related Disorders/ (116132)
26 *Temperance/ (1124)
27 Alcohol Deterrents/ (1464)
28 exp Self-Help Groups/ (10346)
29 "alcohol drinking".mp. (69502)
30 Alcoholism.mp. (85677)
31 dipsomania.mp. (28)
32 "alcohol consumption".mp. (35505)
33 (drink$ adj excess$).tw. (166)
34 (drink$ adj binge).tw. (151)
35 (drink$ adj heavy).tw. (172)
36 (drink$ adj hazard$).tw. (65)
37 (drink$ adj problem$).tw. (1013)
38 (drink$ adj abuse).tw. (15)
39 (drink$ adj misus$).tw. (3)
40 (drink$ adj dependen$).tw. (22)
41 (drink$ adj harm$).tw. (26)
42 (alcohol$ adj excess$).tw. (187)
43 (alcohol$ adj binge).tw. (173)
44 (alcohol$ adj heavy).tw. (58)
45 (alcohol$ adj hazard$).tw. (23)
46 (alcohol$ adj problem$).tw. (4092)
47 (alcohol$ adj abuse).tw. (13751)
48 (alcohol$ adj misus$).tw. (2120)
49 (alcohol$ adj dependen$).tw. (11781)
50 (alcohol$ adj harm$).tw. (143)
51 "alcohol intake".tw. (12132)
52 or/24-51 (203355)
53 23 and 52 (7363)
54 Rehabilitation Centers/ (8187)
55 Health Behavior/ (47408)
56 Health Education/ (61517)
57 Preventive Health Services/ (13277)
58 Preventive Psychiatry/ (236)
59 Directive Counseling/ (2257)
60 exp Behavior Therapy/ (68102)
61 exp Cognitive Therapy/ (23998)
62 exp Evidence-Based Medicine/ (68560)
63 Hospitalization/ (92438)
64 (Referral and Consultation).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (63337)
65 Health Promotion/ (69457)
66 Health Maintenance Organizations/ (16205)
67 "relapse prevention".mp. (2594)
68 "harm reduction".mp. (4164)
69 (naltrexone or acamprosate or disulfiram or opioid-antagonist).tw. (11693)
70 campral.mp. (32)
71 anti?craving.tw. (93)
72 dis?lfiram.tw. (2837)
73 disulfiram.tw. (2837)
74 dissulfiram.tw. (1)
75 disulfuram.mp. (11)

76 "brief intervention".tw. (2179)
77 "motivational interviewing".tw. (2759)
78 "motivational enhancement therapy".tw. (304)
79 "social behavio?r".tw. (7820)
80 "cognitive behavio?ral therapy".tw. (8093)
81 "aversion therapy".tw. (172)
82 "relapse prevention".tw. (2565)
83 "skills training".tw. (4689)
84 treatment.mp. (3915653)
85 or/54-84 (4297698)
86 53 and 85 (3008)
87 limit 86 to yr="2014-Current" (464)
87 limit 86 to yr="2015-Current" (219)
Yield 219 studies
Duplicate 56+5 studies
Total 163 (219-56-5) studies

Search term used in Ovid Embase 1947-Present, updated daily
Search conducted 30/12/2016
1 exp "Costs and Cost Analysis"/ (307717)
2 "Value of Life"/ (122806)
3 Economics/ (226172)
4 Economics, Nursing/ or Economics, Medical/ or exp Economics, Hospital/ or Economics, Pharmaceutical/ (745135)
5 or/1-4 (1000104)
6 (econom$ or cost$ or pric$ or pharmacoeconomic$).ti,ab. (868900)
7 (expenditure$ not energy).ti,ab. (31328)
8 (value adj1 money).ti,ab. (37)
9 budget$.ti,ab. (30426)
10 or/6-9 (897960)
11 5 or 10 (1536285)
12 letter.pt. (970999)
13 editorial.pt. (528311)
14 historical article.pt. (0)
15 12 or 13 or 14 (1499310)
16 11 not 15 (1445834)
17 Animals/ (1549367)
18 Humans/ (11631562)
19 17 not (17 and 18) (1220999)
20 16 not 19 (1425042)
21 (metabolic adj cost).ti,ab. (1168)
22 ((energy or oxygen) adj cost).ti,ab. (3798)
23 20 not (21 or 22) (1420469)
24 *Alcohol Drinking/ (13967)
25 exp Alcohol-Related Disorders/ (125740)
26 *Temperance/ (1100)
27 Alcohol Deterrents/ (668)
28 exp Self-Help Groups/ (13454)
29 "alcohol drinking".mp. (7778)
30 Alcoholism.mp. (132149)
31 dipsomania.mp. (52)
32 "alcohol consumption".mp. (119316)
33 (drink$ adj excess$).tw. (233)
34 (drink$ adj binge).tw. (178)
35 (drink$ adj heavy).tw. (207)
36 (drink$ adj hazard$).tw. (78)
37 (drink$ adj problem$).tw. (1232)

38 (drink$ adj abuse).tw. (17)
39 (drink$ adj misus$).tw. (4)
40 (drink$ adj dependen$).tw. (27)
41 (drink$ adj harm$).tw. (31)
42 (alcohol$ adj excess$).tw. (418)
43 (alcohol$ adj binge).tw. (270)
44 (alcohol$ adj heavy).tw. (78)
45 (alcohol$ adj hazard$).tw. (29)
46 (alcohol$ adj problem$).tw. (4947)
47 (alcohol$ adj abuse).tw. (19000)
48 (alcohol$ adj misus$).tw. (2651)
49 (alcohol$ adj dependen$).tw. (15918)
50 (alcohol$ adj harm$).tw. (220)
51 "alcohol intake".tw. (16147)
52 or/24-51 (259254)
53 23 and 52 (18169)
54 Rehabilitation Centers/ (14480)
55 Health Behavior/ (57248)
56 Health Education/ (92914)
57 Preventive Health Services/ (28005)
58 Preventive Psychiatry/ (3688)
59 Directive Counseling/ (723)
60 exp Behavior Therapy/ (42300)
61 exp Cognitive Therapy/ (43570)
62 exp Evidence-Based Medicine/ (1002636)
63 Hospitalization/ (315576)
64 (Referral and Consultation).mp. (12784)
65 Health Promotion/ (84802)
66 Health Maintenance Organizations/ (18736)
67 "relapse prevention".mp. (3879)
68 "harm reduction".mp. (6106)
69 (naltrexone or acamprosate or disulfiram or opioid-antagonist).tw. (13817)
70 campral.mp. (239)
71 anti?craving.tw. (154)
72 dis?lfiram.tw. (3571)
73 disulfiram.tw. (3571)
74 dissulfiram.tw. (1)
75 disulfuram.mp. (14)
76 "brief intervention".tw. (2179)
77 "motivational interviewing".tw. (3717)
78 "motivational enhancement therapy".tw. (311)
79 "social behavio?r".tw. (9772)
80 "cognitive behavio?ral therapy".tw. (12007)
81 "aversion therapy".tw. (250)
82 "relapse prevention".tw. (3633)
83 "skills training".tw. (6504)
84 treatment.mp. (5818355)
85 or/54-84 (6810673)
86 53 and 85 (8338)
87 limit 86 to yr="2014-Current" (1843)
87 limit 86 to yr="2015-Current" (1139)
Yield 1139 studies
Duplicate 208+13 studies
Total 931 (1139-208-13) studies
Hand searching 3

Appendix 3



scriptcpd

Pattara Leelahavarong

Completed a continuing professional development programme in:

SHIP: Information Governance

Via online distance learning

SHIP

Scottish Health Informatics Programme

With a 100% pass rate in the following assessments:

Legal Concepts Assessment
Legal Framework Assessment
Safe Projects Assessment
Safe Data Assessment
Safe Settings Assessment
Safe Outputs Assessment

Certificate issued: 05 October 2013

Certificate valid until: 05 October 2015

Information Services Division
Area 151A
Gyle Square
1 South Gyle Crescent
EDINBURGH
EH12 9EB
Telephone 0131 275 6000
Fax 0131 275 7606
www.isdscotland.org

NHS National Services Scotland

Miss P Leelahavarong
Research Student
Health Economics and Health Technology Assessment
1 Lilybank Gardens
University of Glasgow
GLASGOW
G12 8RZ

Date 15th October 2014
Your Ref
Our Ref PAC 03/14

Enquiries to Janet Murray
Extension 6954
Direct Line 0131 275 6954
Email janet.murray1@nhs.net

Dear Miss Leelahavarong

Estimation of alcohol-related harms of alcohol-use disorders in Scotland for monitoring and evaluation of alcohol strategy

The Privacy Advisory Committee has considered and approved your application for a data linkage in support of the above study.

Conditions applied: None

Time period: As specified

Points highlighted: The committee highlighted the sensitive nature of the topic under investigation and the detailed information required to support the study. This carries particular risk for privacy and these have to be justified by the public interest in the work. Following our discussion the public interest was clarified.

The approval of the Committee is for a period of 5 years from the date of this letter. Any change to the terms of your application, including changes in data user(s), additional data fields or extension of the time period approved must be requested through Susan Kerr, PAC Administrator on 0131 275 6445 or nss.pac@nhs.net.

Please note that the access to data facilitated by this approval is subject to the satisfactory completion of approved information governance training, which must be updated every 3 years.

Please note that the following details about your application will be published under the following headings on the PAC website at http://www.nhsnss.org/pages/corporate/pac_meetings_and_decision_making.php later this year:

No	Title	Type	Summary	Date sent to PAC	PAC Responses	NSS Decision	Date Completed

In order to progress your request please contact the eDRIS team on telephone 0131 275 7333 or email nss.eDRIS@nhs.net.

Yours sincerely

JG Murray

Dr Janet Murray
Consultant in Public Health Medicine

cc eDRIS

Appendix 4

Self-completed SF-12 Physical and Mental Health Questionnaire in Scottish Health Survey 2003
Please read this carefully
These questions ask for your views about your **health**. This information will help keep track of how you feel and how well you are able to do your usual activities.
Please answer every question by marking one box. If you are unsure about how to answer, please give the best answer you can.

Tick one box
230

		Excellent	Very good	Good	Fair	Poor
Q10	In general, would you say your health is:	1	2	3	4	5

Tick one box on each line

		Yes, limited a lot	Yes, limited a little	No, not limited at all
10.6.1.1 Q11	**Moderate activities** such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	231 2	3
10.6.1.1 Q12	Climbing **several** flights of stairs	1	232 2	3

Tick one box on each line

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

		Yes	No
10.6.1.1 Q13	**Accomplished less** than you would like	1	233 2
10.6.1.1 Q14	Were limited in the **kind** of **work** or other activities	1	234 2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

Tick one box on each line

		Yes	No
10.6.1.1 Q15	**Accomplished less** than you would like	1	235 2
10.6.1.1 Q16	Didn't do work or other activities as **carefully** as usual	1	236 2

Tick one box

		Not at all	A little bit	Moderately	Quite a bit	Extremely
Q17	During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?	1	2	3	4	5

These next questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.
How much of the time during the **past 4 weeks** –

Tick one box on each line

10.6.1.1

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
10.6.1.1 Q18	Have you felt calm and peaceful?	1	2	3	4	5	238 6 239
Q19	Did you have a lot of energy?	1	2	3	4	5	6 240
Q20	Have you felt downhearted and low?	1	2	3	4	5	6 241
Q21	During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?	1	2	3	4	5	6

Appendix 5

TABLE 2. The SF-6D (SF-12 version)

	Physical Functioning		**Pain**
1	Your health does not limit you in moderate activities.	1	You have pain that does not interfere with your normal work (both outside the home and housework) at all
2	Your health limits you a little in moderate activities.	2	You have pain that interferes with your normal work (both outside the home and housework) a little bit
3	Your health limits you a lot in moderate activities.	3	You have pain that interferes with your normal work (both outside the home and housework) moderately
		4	You have pain that interferes with your normal work (both outside the home and housework) quite a bit
		5	You have pain that interferes with your normal work (both outside the home and housework) extremely
	Role limitations		**Mental health**
1	You have no problems with your work or other regular daily activities as a result of your physical health or any emotional problems	1	You feel downhearted and low none of the time
2	You are limited in the kind of work or other activities as a result of your physical health	2	You feel downhearted and low a little of the time
3	You accomplish less than you would like as a result of emotional problems	3	You feel downhearted and low some of the time
4	You are limited in the kind of work or other activities as a result of your physical health and accomplish less than you would like as a result of emotional problems	4	You feel downhearted and low most of the time
		5	You feel downhearted and low all of the time
	Social functioning		**Vitality**
1	Your health limits your social activities none of the time	1	You have a lot of energy all of the time
2	Your health limits your social activities a little of the time	2	You have a lot of energy most of the time
3	Your health limits your social activities some of the time	3	You have a lot of energy some of the time
4	Your health limits your social activities most of the time	4	You have a lot of energy a little of the time
5	Your health limits your social activities all of the time	5	You have a lot of energy none of the time

Source: Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. Med Care2004 Sep;42(9):851-9.

Appendix 6

Ethics Committee

Institute for the Development of Human Research Protections (IHRP)

Building 8 Floor 7 Room 702 Department of Medical Science Ministry Public Health Nonthaburi Thailand 11000

Certificate of Approval

Title of Project: Development and validation of alcohol-related harms prediction model for monitoring and evaluation of alcohol consumption control programmes. (Version 1/291057)

Principal Investigator: Pattara Leelahavarong

Responsible Organization: Health Intervention and Technology Assessment Program

The Ethics Committee of Institute for the Development of Human Research Protections (IHRP) had reviewed the research proposal. Concerning on scientific, ICH-GCP and ethical issues, the committee has approved for the implementation of the research study mentioned above.

(Dr.Vichai Chokevivat)	(Dr.Pramote Stienrut)
Chairman	Committee and Secretary

Date of First Meeting: November 27, 2014

Date of Approval: November 27, 2014

Appendix 7

Thai Expert Consultation Meeting minutes
Research title "Development and validation of alcohol-use disorder prediction model for monitoring and evaluation of alcohol consumption control programmes"
HITAP meeting room I, Health Intervention and Technology Assessment Programme (HITAP)
26th November 2014 at 1:30-3:30 pm

Participants:

1. Prof. Dr. Paibul Suriyawongpaisal	Department of Community Medicine, Faculty of Medicine, Mahidol University
2. Assoc. Prof. Dr. Sawitree Ausanangkornchai	Epidemiology Unit, Faculty of Medicine, Prince of Songkla University
3. Dr. Nopporn Tantirangsee	Songkhlarajanagarindra Psychiatric Hospital
4. Dr. Piya Hanvoravongchai	Department of Preventive and Social Medicine, Faculty of Medicine, Chulalongkorn University
5. Assist. Prof. Montarat Thavorncharoensap	Faculty of Pharmacy, Mahidol University
6. Dr. Yot Teerawattananon	HITAP
7. Dr. Sripen Tantivess	HITAP
8. Pattara Leelahavarong	HITAP
9. Waranya Rattanawipapong	HITAP
10. Varit Chantarastapornchit	HITAP

Meeting objectives

1. To discuss and comment on the research methods and preliminary results of analyses using Scottish linkage dataset.
2. To consult about the possibility and availability of Thai dataset to do a methodological transferability.
3. To recommend the further applications of research methods and findings to conduct the future research for evaluation and monitoring the alcohol consumption control programmes and another health promotion interventions in Thailand

Meeting summary

I. Researcher's presentation

- This study aims to develop a surrogate outcome of alcohol consumption control interventions, which the outcome provides early and accurate prediction of both a clinical endpoint and the effect of intervention on this endpoint, and then lifetime quality-adjusted life years (QALYs) of different drinking status would be estimated in the Thai context. The linkage data between Scottish Health Surveys (SHeS) and Scottish Morbidity Records (SMRs) would be used for

analysis. The preliminary results showed that Alcohol Use Disorders Identification Test (AUDIT) associated with HRQoL in term of SF-6D utility index as well as the risk of alcohol-related hospitalisations and deaths.

II. Discussion and comments

- The foundation and justification of using AUDIT should be well described i.e. the validation of using AUDIT to measure the drinking status in the Thai setting, the importance of each increasing scale in each component (not only overall score), the cardinal scale property of AUDIT, the comparison among alcohol drinking measurement.
- Binge drinking (3rd item of AUDIT) and each component of AUDIT should be also investigated the association with alcohol-related harms.
- This study aims to estimate the lifetime alcohol-related harms and convert to QALYs classified by drinking status. Nonetheless, the limitation of cross-sectional design which the participants' drinking status as well as AUDIT score measured in SHeS could not be followed up the change of drinking status over lifetime period, so the experts suggested that the developed model for QALY estimation should take into account a changeable drinking pattern overtime.
- When this study could estimate the QALYs of drinkers in the Thai context, an external validation of alcohol-related harm prediction model might be conducted for example, using a survey design to interview the drinking status and AUDIT as well as QALYs directly, or comparing to an existing cohort in Thailand. However, the agreement of Thai experts suggested to conduct a further study for the external validation and include the study plan in discussion of the current study.
- Since AUDIT is a behaviour measurement related to alcohol consumption and alcohol use disorder, the implication of AUDIT for monitoring and evaluation of any health promotion intervention might be the intervention which aims to change particularly the behaviour of target population. Nevertheless, many health promotion programmes aim for knowledge and attitude changed, so the further study might include the association between knowledge/attitude changed and the developed behaviour surrogate outcome.
- The association of alcohol drinking, alcohol-related harms, and deprivation is interesting, and it may be a further health research in Thailand.
- Relevant and existing data in Thailand: 1) the national epidemiological survey of mental health 2013-2014 (N~5,000) conducted by Department of Mental Health, Ministry of Public Health using Composite International Diagnostic Interview or CIDI, which an alcohol abuse and alcohol dependence were diagnosed, as well as EQ-5D-5L of respondents were also collected (Thai tariff can be applied for utility index calculation); 2) National Health Examination Survey V (2013) conducted by National Health Examination Survey Office, which alcohol consumption was included; 3) a cohort in Ubonrachathani province (N~20,000); 4) a hospitalisation records of Central Office of Health Care (ICD-10 of alcohol-related conditions might be under-reported); and 5) baseline mortality and alcohol-related death reported by Thai Burden of Diseases (BOD).

- In summary, the Thai experts agreed with the methodology using Scottish linkage dataset, and the main suggestions surrounding analyses were 1) whether using another measurements of alcohol drinking e.g. binge drinking or using each component of AUDIT not only overall score would affect to the association between those measurements and alcohol-related harms compared to using overall AUDIT score, and 2) according to the limited study period and data sources in Thailand, the completed transferability of this study to the Thai context would likely need the further study in Thailand after finished PhD study, so almost all of Thai experts suggested to add a thesis chapter to describe the further study plan and framework rather than the final results in the Thai context with substantial assumptions.

Appendix 8

Uncertainty in decision analytic model

In healthcare decision-making, decision analysis provides a statistical or mathematical process that brings together multiple sources of evidence on a range of parameters in order to estimate the costs and outcomes of all alternative interventions. Decision analysis provides a systematic and explicit approach to decision-making under conditions of uncertainty (Briggs, 2000). It is intended to assist conventional decision-making. Although analysts seek to develop models and incorporate data that most accurately inform the costs and outcomes associated with a particular disease and intervention, some degree of uncertainty is present in the majority of models; uncertainty about the true parameter values, the type of model used and the model results. More formally the dimensions of uncertainty have been categorised as parameter, heterogeneity, methodological and structural (Briggs, 2000). Each dimension requires to be dealt with differently. Assessing heterogeneity employ methods to adjust for patient characteristics, geographical location or to compute cost-effectiveness results for particular sub-groups of patients or locations (Sculpher et al., 2004). Moreover, it requires consideration whether other factors inherent to these groups influence the study outcomes by confounding or overriding the actual treatment effects, i.e. different age groups, differences in gender or disease specification (NICE, 2013). Methodological uncertainty refers to uncertainty regarding whether the methods used were the most appropriate (Briggs, 2000). Methodological uncertainties can be dealt with through the use of a reference case for appropriate methodology, i.e. by following good practice guidelines for undertaking modelling (ISPOR, 2014). Structural uncertainty is classified into the following general types: (i) inclusion/exclusion of potentially relevant comparators; (ii) inclusion/exclusion of potentially relevant events; (iii) statistical models to estimate specific parameters and (iv) clinical uncertainty or lack of clinical evidence (Bojke et al., 2009). Uncertainty regarding the structure of the model can be dealt with

by one-way sensitivity analyses and scenario analyses, modifying one or more structural aspects or assumptions of the model and determining the impact on outcomes. More recently it has been suggested that a formal framework is required to addressed structural uncertainty, whereby a global model could be developed including parameters which encompass all possible structural choices so that they can be addressed using probabilistic methods (Jackson et al., 2011).

Parameter uncertainty refers to uncertainty in the point estimates used to reflect the specific parameters in the model, i.e. uncertainty in the mean utility value assigned to a specific disease group, or uncertainty in the probability of an event. A decision model can explicitly represent this uncertainty and quantify it through the use of probabilistic sensitivity analysis (PSA), which is detailed in the next section (Briggs, 2000, Fenwick et al., 2001, Briggs et al., 2006a). PSA can be conducted for as many uncertain parameters as the model may contain, concurrently. Uncertainty about a parameter is represented by a probability distribution. The choice of distribution is informed by the type and shape of the data observed, for example cost data are usually represented by gamma distributions and probability data by beta distributions (Briggs et al., 2006a). Markov Chain Monte Carlo (MCMC) simulation methods are then used to simulate the expected costs and outcomes of the various interventions, by sampling from the distributions that feed into the estimation. In this way, PSA enables uncertainty surrounding all input parameters to be propagated through the decision model in order that uncertainty surrounding the decision itself can be quantified. Finally, decision uncertainty should also be explored. Decision uncertainty refers to the level of uncertainty in the cost-effectiveness outcome from the model, i.e. uncertainty in the estimated cost-effectiveness of the treatment in comparison to the alternative(s) (Fenwick et al., 2001, Briggs et al., 2006b).

Assessing parameter uncertainty

In a probabilistic sensitivity analysis (PSA), uncertainty in the mean parameter estimates is accounted for by assigning a distribution to each parameter and drawing a random estimate from that distribution to represent the point estimate (Briggs et al., 2006a). By drawing randomly from the parameter distributions simultaneously for all parameters in the model and repeating this random draw numerous times (in a Monte Carlo simulation) uncertainty in the parameter estimates is accounted for cost, effect and cost-effectiveness results from the model can be calculated for each simultaneous random draw (iteration). The average cost, effect and cost-effectiveness across all the iterations in the Monte Carlo simulation are taken to represent the probabilistic outcomes which account for uncertainty in the input parameters. Using any number of iterations greater than 1000 is generally considered to be acceptable to reflect uncertainty in the model parameters. If there are negligible or minimal changes to the incremental cost and incremental effectiveness outcomes between variations in the number of iterations then the outcomes can be considered stable.

Defining and choosing distributions for parameters

In dealing with parameter uncertainty, the model parameters need to represent the sampling distribution. This has important implications for the choice of distribution for any of the parameters to represent the uncertainty in any parameter of the model, which vary depending on the family or from of distribution (Briggs et al., 2006a). However, the probability distribution that represents uncertainty in a decision analytic model is not chosen randomly but decided based on the type of data, the parameter type and estimation process as follows:

Normal distribution: The most commonly used continuous distribution is the normal distribution. The Standard Normal Distribution has an expected mean value of zero, and a variance of one N(0,1). Therefore, a random variable

(parameter) on the normal distribution is of any value between negative and positive infinity (-∞, ∞). Many distributions can be approximated to the normal distribution under an assumption based on the central limit theorem which assumes that as a sample size gets very large (tending towards infinity) the sampling distribution of the mean will be normally distributed regardless of the underlying distribution of the data. Therefore, in a decision analytic model, the normal distribution can be considered a candidate for any of the parameters in the model; however, this is only as the parameter which is of a large enough sample size to justify a normal assumption.

Log normal distribution: The log normal distribution is a continuous probability distribution that ranges from zero to positive infinity (0, ∞) and is positively skewed. This distribution does not cover any negative values. This distribution is suitable for parameters that are non-negative as well as highly skewed or are multiplicative, such as ratios. A normal distribution is generated if the natural logarithms of the parameters of such a distribution are calculated.

Beta distribution: In probability theory and statistics, the beta distribution is employed to model the proportion of successes (n) in a binomial trial and define the interval (0,1). Two positive shape parameters that appear as exponents of the random variable and control the shape of the distribution are α and ß. α is the number of events that occur and ß is the number of non-events.

Dirichlet distribution: The Dirichlet distribution, being multivariate in nature, is generally considered to be the multinomial extension of the beta distribution with one parameter per category. It is thought of as flexible and convenient, computationally, as its components take values (0,1) (Briggs et al., 2003).

Gamma distribution: The gamma distribution is useful for continuous variables, particularly those considered to be highly skewed. It is constrained

within the interval zero to positive infinity (0, ∞). Gamma distribution is represented by α and ß.

For choosing distributions for parameters, the common distributions in PSA are normal, log-normal, beta and gamma distributions (Briggs et al., 2006a). First, probability parameters can only take values between zero and one (0,1). Beta distributions are commonly representative of such parameters as prevalence, diagnostic test accuracy, and the probabilities exclusive events must sum to one. Uncertainty in this probability can be presented by two parameters, α and ß, as mentioned in the previous section, ß = (sample size (n) – the number of events occurring (α)). Normally, α and n are reported in publications, and these are used to calculate the ß for the beta distribution. On the other hand, as opposed to binomial data, multinomial data with numerous categories, each represented by proportions that sum to one, are appropriate for the Dirichlet distribution (Briggs et al., 2003). If the overall sample size and the number of events of interest for each category are reported in a publication, the data can then be used to calculate proportions for each category to fit the Dirichlet distribution.

Second, costs data are calculated from resource usage, weighted by unit costs (Briggs et al., 2006a). Therefore, cost parameters should not be lower than zero, as it is not possible to have a negative result, although they can range up to infinity. When considering which distribution best fits the costs parameter, gamma distribution can be selected as it is constrained to value zero and upward to infinity (0, ∞). If cost estimates of a suitably large sample are found to be symmetric around the mean, it can be assumed that the central limit theorem applies and a normal distribution fitted to the data. However, if the data is highly skewed, a more characteristic situation for cost data, both log-normal and gamma distribution are used to fit the distribution.

Third, utility can be suited to the Beta distribution only if it is appropriate to assume that the utility range is between close to zero and close

to one (Briggs et al., 2006a). However, in cases of severe life-threatening illness, the utility can be very low or negative utility and so utility ranges between negative infinity and one (-∞, 1). Therefore, the beta distribution should be avoided in such cases. When the transformation of disutility = 1 - utility, where disutility is a utility decrement, the distribution is constrained on the scale zero to infinity (0, ∞) and is better fitted to a Gamma or Log-normal distribution.

In cases where only partial evidence has been reported, i.e. a mean value with no standard error, assumptions can be used to determine an appropriate standard error (which is large enough to reflect a wide range of uncertainty). Additionally, if 95% confidence intervals have been reported rather than a specification of the standard error, then the standard error can be calculated using the 95% confidence limits.

Appendix 9

Male – 1. cause specific hazard model of first hospitalisation with wholly alcohol-attributable conditions

Cholesky decomposition

	age	AUDIT	Binge	CVD	DM	Cigarettes /day	Phys. actv. (Low)	Phys. actv. (Med)	Phys. actv. (High)	SIMD (2)	SIMD (3)	SIMD (4)	SIMD (Least Deprived)	Other Hos LastYr	Other Hos Over LastYr	GHQ (1-3)	GHQ (4+ worse)	Constant	Gamma
age	0.009	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
AUDIT	0.003	0.019	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Binge	0.018	-0.191	0.259	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CVD	-0.101	-0.011	0.004	0.268	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
DM	-0.020	0.016	0.029	-0.137	1.014	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Cigarettes /day	0.000	-0.001	-0.001	0.000	0.000	0.005	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Low)	0.025	-0.007	-0.018	0.025	0.020	0.066	0.394	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Med)	0.058	-0.008	-0.012	0.057	0.025	0.044	0.184	0.299	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (High)	0.104	-0.026	-0.037	0.072	0.030	0.069	0.182	0.130	0.264	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(2)	-0.005	0.011	0.004	0.001	0.000	0.009	-0.016	-0.018	0.002	0.340	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(3)	-0.014	0.023	0.020	-0.002	0.001	-0.041	-0.003	-0.001	0.005	0.115	0.334	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(4)	-0.009	0.034	0.015	-0.002	0.004	0.027	-0.016	-0.009	-0.013	0.116	0.082	0.364	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD (Least Deprived)	-0.021	0.025	0.017	0.002	0.003	0.038	-0.021	-0.017	-0.015	0.116	0.082	0.058	0.378	0.000	0.000	0.000	0.000	0.000	0.000
OtherHos LastYr	-0.023	0.019	0.027	-0.034	-0.011	-0.009	0.033	0.021	0.012	-0.010	-0.011	0.014	0.015	0.423	0.000	0.000	0.000	0.000	0.000
OtherHos OverLastYr	-0.012	0.015	0.013	-0.010	-0.009	-0.031	0.024	0.015	-0.008	0.004	-0.001	0.007	0.011	0.122	0.247	0.000	0.000	0.000	0.000
GHQ (1-3)	0.024	-0.019	-0.002	-0.001	0.003	-0.046	0.019	0.010	0.009	0.007	-0.022	0.011	0.010	-0.021	-0.007	0.307	0.000	0.000	0.000
GHQ (4+worse)	0.030	-0.064	-0.003	-0.016	0.007	-0.021	0.028	0.023	0.021	0.015	0.029	0.030	0.022	-0.027	-0.005	0.114	0.263	0.000	0.000
Constant	-0.486	-0.073	-0.114	-0.128	-0.040	-0.082	-0.196	-0.131	-0.083	-0.121	-0.083	-0.073	-0.060	-0.126	-0.153	-0.117	-0.090	0.173	0.000
Gamma	0.005	0.001	-0.002	0.002	0.001	0.000	-0.002	-0.003	-0.001	0.000	0.001	0.000	0.000	0.005	0.004	0.000	0.002	-0.023	0.023

Male – 2. cause specific hazard model of first hospitalisation with partly alcohol-attributable conditions
Cholesky decomposition

	age	AUDIT	Binge	CVD	DM	Cigarettes /day	Phys. actv. (Low)	Phys. actv. (Med)	Phys. actv. (High)	SIMD (2)	SIMD (3)	SIMD (4)	SIMD (Least Deprived)	Other Hos LastYr	Other Hos Over LastYr	GHQ (1-3)	GHQ (4+ worse)	Constant	Gamma
age	0.004	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
AUDIT	0.002	0.013	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Binge	0.009	-0.093	0.109	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CVD	-0.035	0.003	0.006	0.113	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
DM	0.003	0.007	0.006	-0.049	0.211	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Cigarettes /day	0.000	-0.001	-0.001	0.000	0.000	0.004	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Low)	0.018	-0.004	-0.014	0.009	0.009	0.008	0.175	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Med)	0.026	-0.006	-0.009	0.022	0.014	0.006	0.077	0.120	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (High)	0.044	-0.010	-0.016	0.027	0.017	0.012	0.076	0.066	0.127	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(2)	-0.002	0.001	0.006	-0.003	0.000	0.004	-0.001	-0.007	-0.003	0.167	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(3)	-0.003	0.002	0.011	-0.001	0.002	0.007	-0.001	-0.005	-0.004	0.081	0.129	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(4)	-0.002	0.004	0.009	-0.002	0.003	0.014	-0.002	-0.005	-0.010	0.081	0.055	0.147	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD (Least Deprived)	-0.005	-0.006	0.006	0.001	0.004	0.019	-0.004	-0.010	-0.008	0.081	0.055	0.028	0.132	0.000	0.000	0.000	0.000	0.000	0.000
OtherHos LastYr	-0.013	0.005	0.011	-0.020	-0.009	0.003	0.015	0.018	0.010	-0.004	-0.004	0.006	0.005	0.169	0.000	0.000	0.000	0.000	0.000
OtherHos OverLastYr	-0.009	0.003	0.004	-0.010	-0.007	0.000	0.009	0.009	0.003	-0.001	0.002	0.003	0.002	0.055	0.104	0.000	0.000	0.000	0.000
GHQ (1-3)	0.012	-0.002	0.003	0.001	0.002	-0.011	0.007	0.007	0.004	0.004	-0.002	0.003	0.004	-0.011	0.003	0.129	0.000	0.000	0.000
GHQ (4+worse)	0.020	-0.019	0.003	-0.003	0.002	-0.010	0.010	0.013	0.008	0.005	0.011	0.008	0.007	-0.017	0.001	0.032	0.165	0.000	0.000
Constant	-0.277	-0.044	-0.043	-0.066	-0.027	-0.032	-0.077	-0.061	-0.026	-0.082	-0.057	-0.033	-0.028	-0.061	-0.065	-0.033	-0.020	0.074	0.000
age	0.003	0.000	-0.001	0.002	0.001	-0.001	-0.001	-0.002	0.000	0.000	0.000	0.000	0.000	0.003	0.002	0.000	0.000	-0.009	0.009

Male – 3. cause specific hazard model of first hospitalisation with non-emergency& non-CVD conditions
Cholesky decomposition

	age	AUDIT	Binge	BMI (over weigh t)	BMI (obesi ty)	CVD	DM	Cigarettes/ day	Phys. actv. (Low)	Phys. actv. (Med)	Phys. actv. (High)	SIMD (2)	SIMD (3)	SIMD (4)	SIMD (Least Deprived)	Other Hos Last Yr	Other Hos Over LastYr	GHQ (1-3)	GHQ (4+ worse)	Constant	Gamma
age	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
AUDIT	0.001	0.004	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Binge	0.001	-0.026	0.029	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
BMI (over weight)	-0.004	0.001	0.000	0.035	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
BMI (obesity)	-0.003	0.000	0.000	0.022	0.034	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CVD	-0.011	0.001	0.002	-0.003	-0.004	0.032	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
DM	0.000	0.003	0.002	0.000	-0.006	-0.018	0.062	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Cigarettes /day	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Low)	0.004	-0.001	-0.003	0.001	0.000	0.003	0.003	0.001	0.052	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Med)	0.006	-0.002	-0.002	0.001	0.001	0.006	0.005	0.000	0.025	0.035	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (High)	0.011	-0.003	-0.004	0.003	0.003	0.008	0.006	0.002	0.024	0.020	0.029	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(2)	0.000	0.000	0.001	-0.001	0.000	0.000	0.000	0.002	-0.001	-0.001	-0.001	0.044	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(3)	-0.001	0.000	0.002	-0.002	0.000	0.000	0.000	0.003	-0.001	-0.001	-0.001	0.023	0.037	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(4)	-0.001	0.000	0.001	-0.001	0.000	0.000	0.001	0.005	-0.001	-0.001	-0.002	0.023	0.013	0.035	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD (Least Deprived)	-0.002	-0.002	0.001	-0.002	0.001	0.000	0.001	0.006	-0.001	-0.002	-0.002	0.023	0.013	0.009	0.037	0.000	0.000	0.000	0.000	0.000	0.000
OtherHos LastYr	-0.003	0.001	0.002	-0.002	-0.001	-0.005	-0.003	0.000	0.004	0.004	0.002	-0.001	0.000	0.002	0.002	0.044	0.000	0.000	0.000	0.000	0.000
OtherHos OverLastYr	-0.001	0.000	0.001	-0.002	-0.001	-0.002	-0.002	0.000	0.002	0.002	0.000	0.000	0.000	0.001	0.001	0.016	0.028	0.000	0.000	0.000	0.000
GHQ (1-3)	0.003	0.000	0.001	0.001	0.000	0.000	0.000	-0.001	0.001	0.001	0.001	0.001	0.000	0.001	0.001	-0.002	0.001	0.033	0.000	0.000	0.000
GHQ (4+worse)	0.004	-0.004	0.001	0.002	-0.001	-0.001	0.000	-0.003	0.002	0.003	0.003	0.001	0.002	0.002	0.001	-0.004	0.001	0.010	0.041	0.000	0.000
Constant	-0.059	-0.012	-0.010	-0.021	-0.009	-0.015	-0.008	-0.010	-0.025	-0.019	-0.010	-0.023	-0.014	-0.011	-0.007	-0.017	-0.017	-0.010	-0.006	0.020	0.000
Gamma	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.000	0.000	-0.003	0.003

Male – 4. cause specific hazard model of first hospitalisation with non-emergency& CVD conditions
Cholesky decomposition

	age	AUDIT	Binge	BMI (over weight)	BMI (obesity)	CVD	DM	Cigarettes /day	Phys. actv. (Low)	Phys. actv. (Med)	Phys. actv. High)	SIMD (2)	SIMD (3)	SIMD (4)	SIMD (Least Deprived)	Other Hos LastYr	OtherHos OverLastYr	GHQ (1-3)	GHQ (4+worse)	Constant	Gamma
age	0.005	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
AUDIT	0.003	0.019	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Binge	0.007	-0.128	0.137	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
BMI (over weight)	-0.005	-0.002	0.000	0.163	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
BMI (obesity)	0.001	0.005	-0.007	0.119	0.152	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CVD	-0.046	0.005	0.009	-0.013	-0.013	0.144	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
DM	0.002	0.008	0.008	-0.004	-0.027	-0.039	0.205	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Cigarettes /day	0.001	-0.001	-0.001	0.001	0.000	0.000	0.000	0.006	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Low)	0.022	-0.006	-0.017	0.002	-0.003	0.007	0.010	0.009	0.194	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Med)	0.033	-0.011	-0.010	0.004	0.003	0.022	0.015	0.005	0.082	0.146	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (High)	0.053	-0.016	-0.018	0.011	0.008	0.029	0.019	0.011	0.082	0.068	0.155	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(2)	-0.005	-0.001	0.005	-0.001	-0.003	-0.002	0.002	0.007	-0.001	-0.009	-0.004	0.195	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(3)	-0.002	-0.002	0.011	-0.007	-0.001	-0.001	0.006	0.007	-0.002	-0.003	-0.005	0.089	0.169	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(4)	-0.004	0.000	0.008	-0.002	0.002	-0.002	0.005	0.019	-0.002	-0.006	-0.013	0.089	0.057	0.154	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD (Least Deprived)	-0.007	-0.013	0.003	-0.006	0.005	0.002	0.009	0.023	-0.006	-0.015	-0.010	0.089	0.057	0.042	0.171	0.000	0.000	0.000	0.000	0.000	0.000
OtherHos LastYr	-0.017	0.008	0.013	-0.013	-0.003	-0.023	-0.013	0.003	0.017	0.022	0.017	-0.006	-0.005	0.007	0.004	0.181	0.000	0.000	0.000	0.000	0.000
OtherHos Over LastYr	-0.012	0.006	0.004	-0.011	-0.007	-0.012	-0.011	0.001	0.011	0.013	0.007	-0.001	0.003	0.004	0.002	0.089	0.125	0.000	0.000	0.000	0.000
GHQ (1-3)	0.013	-0.001	0.004	0.001	0.000	0.001	0.003	-0.011	0.008	0.009	0.004	0.004	-0.003	0.005	0.004	-0.016	0.008	0.153	0.000	0.000	0.000
GHQ (4+worse)	0.023	-0.022	0.004	0.006	0.005	-0.005	0.003	-0.010	0.012	0.016	0.013	0.007	0.012	0.011	0.007	-0.023	0.006	0.044	0.167	0.000	0.000
Constant	-0.345	-0.054	-0.045	-0.101	-0.032	-0.104	-0.037	-0.039	-0.084	-0.066	-0.035	-0.089	-0.060	-0.049	-0.030	-0.095	-0.070	-0.048	-0.029	0.087	0.000
Gamma	0.004	0.000	-0.001	0.001	0.000	0.002	0.001	-0.001	-0.002	-0.002	0.000	0.000	0.000	0.000	0.000	0.004	0.002	0.001	0.000	-0.011	0.012

Male – 5. cause specific hazard model of first hospitalisation with emergency & Non-CVD conditions
Cholesky decomposition

	age	AUDIT	Binge	BMI (over weight)	BMI (obesity)	CVD	DM	Cigarettes /day	Phys. actv. (Low)	Phys. actv. (Med)	Phys. actv. (High)	SIMD (2)	SIMD (3)	SIMD (4)	SIMD (Least Deprived)	Other Hos LastYr	Other Hos Over LastYr	GHQ (1-3)	GHQ (4+worse)	Constant	Gamma
age	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
AUDIT	0.001	0.005	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Binge	0.001	-0.034	0.038	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
BMI (over weight)	-0.006	0.000	0.001	0.045	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
BMI (obesity)	-0.004	0.000	0.000	0.026	0.045	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CVD	-0.015	0.001	0.002	-0.004	-0.005	0.042	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
DM	-0.001	0.003	0.003	-0.001	-0.008	-0.022	0.072	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Cigarettes /day	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.002	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Low)	0.005	-0.001	-0.004	0.001	0.000	0.004	0.005	0.002	0.066	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Med)	0.008	-0.002	-0.003	0.002	0.002	0.008	0.007	0.001	0.025	0.045	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (High)	0.015	-0.004	-0.005	0.004	0.004	0.011	0.008	0.003	0.025	0.023	0.039	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(2)	0.000	0.000	0.001	-0.002	0.000	-0.001	0.000	0.003	-0.001	-0.002	-0.001	0.053	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(3)	-0.001	0.000	0.003	-0.003	0.000	-0.001	0.001	0.004	-0.001	-0.001	-0.001	0.025	0.049	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(4)	-0.001	0.001	0.002	-0.002	0.000	-0.001	0.001	0.006	-0.002	-0.002	-0.003	0.025	0.014	0.047	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD (Least Deprived)	-0.002	-0.002	0.002	-0.003	0.001	0.000	0.001	0.008	-0.002	-0.003	-0.003	0.025	0.014	0.011	0.050	0.000	0.000	0.000	0.000	0.000	0.000
OtherHos LastYr	-0.003	0.001	0.003	-0.003	-0.001	-0.007	-0.004	-0.001	0.005	0.006	0.003	-0.001	0.000	0.002	0.002	0.058	0.000	0.000	0.000	0.000	0.000
OtherHos Over LastYr	-0.001	0.001	0.001	-0.002	-0.001	-0.003	-0.002	-0.001	0.003	0.003	0.000	0.000	0.001	0.001	0.001	0.022	0.036	0.000	0.000	0.000	0.000
GHQ (1-3)	0.004	0.000	0.001	0.001	0.000	0.000	0.001	-0.002	0.001	0.002	0.001	0.001	-0.001	0.001	0.001	-0.003	0.001	0.044	0.000	0.000	0.000
GHQ (4+worse)	0.005	-0.007	0.001	0.003	0.001	-0.002	0.001	-0.004	0.003	0.004	0.004	0.002	0.003	0.003	0.002	-0.005	0.000	0.013	0.050	0.000	0.000
Constant	-0.074	-0.015	-0.014	-0.024	-0.012	-0.019	-0.011	-0.012	-0.025	-0.023	-0.012	-0.025	-0.015	-0.013	-0.009	-0.023	-0.022	-0.013	-0.009	0.025	0.000
Gamma	0.001	0.000	0.000	0.000	0.000	0.001	0.000	0.000	0.000	-0.001	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.000	0.000	-0.003	0.003

Male – 6. cause specific hazard model of first hospitalisation with emergency & CVD conditions

Cholesky decomposition

	age	AUDIT	Binge	BMI (over weight)	BMI (obesity)	CVD	DM	Cigarettes /day	Phys. actv. (Low)	Phys. actv. (Med)	Phys. actv. (High)	SIMD (2)	SIMD (3)	SIMD (4)	SIMD (Least Deprived)	Other Hos LastYr	Other Hos Over LastYr	GHQ (1-3)	GHQ (4+worse)	Constant	Gamma
age	0.004	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
AUDIT	0.002	0.013	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Binge	0.007	-0.090	0.099	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
BMI (over weight)	-0.003	-0.001	0.002	0.122	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
BMI (obesity)	0.002	0.000	0.001	0.090	0.107	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CVD	-0.030	0.004	0.005	-0.008	-0.010	0.099	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
DM	0.004	0.005	0.005	-0.003	-0.019	-0.036	0.141	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Cigarettes /day	0.000	-0.001	0.000	0.001	0.000	0.000	0.000	0.002	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Low)	0.016	-0.003	-0.011	0.001	-0.003	0.006	0.009	0.010	0.140	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Med)	0.023	-0.006	-0.006	0.002	0.002	0.017	0.014	0.009	0.058	0.103	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (High)	0.038	-0.010	-0.012	0.007	0.006	0.021	0.016	0.013	0.058	0.049	0.113	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(2)	-0.004	0.001	0.006	-0.002	-0.003	-0.002	0.000	0.001	-0.002	-0.007	-0.003	0.131	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(3)	-0.004	-0.001	0.009	-0.004	-0.002	-0.001	0.003	-0.006	0.000	-0.003	-0.004	0.068	0.117	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(4)	-0.004	0.001	0.007	-0.002	-0.001	-0.002	0.003	0.008	-0.002	-0.005	-0.010	0.068	0.037	0.117	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD (Least Deprived)	-0.006	-0.009	0.003	-0.004	0.003	0.001	0.005	0.011	-0.004	-0.010	-0.008	0.068	0.037	0.026	0.128	0.000	0.000	0.000	0.000	0.000	0.000
OtherHos LastYr	-0.011	0.004	0.010	-0.007	-0.003	-0.018	-0.009	0.006	0.013	0.015	0.010	-0.004	-0.003	0.005	0.004	0.146	0.000	0.000	0.000	0.000	0.000
OtherHos Over LastYr	-0.009	0.002	0.003	-0.007	-0.004	-0.010	-0.008	-0.003	0.008	0.009	0.004	-0.001	0.001	0.003	0.002	0.057	0.091	0.000	0.000	0.000	0.000
GHQ (1-3)	0.008	-0.005	0.002	0.001	-0.001	0.000	0.001	-0.015	0.008	0.007	0.004	0.004	-0.004	0.004	0.003	-0.011	0.002	0.111	0.000	0.000	0.000
GHQ (4+worse)	0.019	-0.012	0.004	0.003	0.003	-0.003	0.002	-0.008	0.011	0.010	0.009	0.006	0.009	0.008	0.006	-0.015	0.002	0.029	0.131	0.000	0.000
Constant	-0.259	-0.037	-0.035	-0.082	-0.025	-0.061	-0.028	-0.020	-0.060	-0.045	-0.023	-0.069	-0.038	-0.031	-0.021	-0.062	-0.059	-0.031	-0.018	0.063	0.000
Gamma	0.003	0.000	-0.001	0.000	0.000	0.002	0.001	-0.001	-0.001	-0.002	0.000	0.000	0.000	0.000	0.000	0.003	0.002	0.000	0.000	-0.008	0.008

Male – 7. cause specific hazard model of first event as alcohol-related death

Cholesky decomposition

	age	AUDIT	Binge	CVD	DM	Cigarettes /day	Phys. actv. (Low)	Phys. actv. (Med)	Phys. actv. (High)	SIMD (2)	SIMD (3)	SIMD (4)	SIMD (Least Deprived)	Other Hos LastYr	Other Hos Over LastYr	GHQ (1-3)	GHQ (4+worse)	Constant	Gamma
age	0.011	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
AUDIT	0.005	0.026	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Binge	0.029	-0.226	0.312	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CVD	-0.115	0.002	0.021	0.335	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
DM	-0.007	0.014	0.034	-0.170	0.492	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Cigarettes /day	0.000	-0.002	-0.001	0.000	0.001	0.009	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Low)	0.035	-0.005	-0.033	0.025	0.041	0.022	0.579	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Med)	0.073	0.000	-0.021	0.061	0.058	0.000	0.151	0.373	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (High)	0.135	-0.026	-0.042	0.082	0.072	0.030	0.150	0.178	0.312	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(2)	-0.002	0.009	0.016	-0.002	0.006	0.029	-0.012	-0.024	-0.007	0.366	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(3)	-0.014	0.023	0.037	-0.010	0.011	-0.012	-0.009	-0.009	-0.009	0.172	0.534	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(4)	-0.010	0.024	0.025	-0.013	0.015	0.046	-0.014	-0.017	-0.028	0.172	0.064	0.417	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD (Least Deprived)	-0.019	0.011	0.025	-0.001	0.012	0.065	-0.020	-0.030	-0.028	0.172	0.064	0.074	0.439	0.000	0.000	0.000	0.000	0.000	0.000
OtherHos LastYr	-0.018	0.020	0.033	-0.037	-0.034	-0.002	0.029	0.036	0.022	-0.005	-0.004	0.017	0.019	0.422	0.000	0.000	0.000	0.000	0.000
OtherHos Over LastYr	-0.008	0.015	0.011	-0.020	-0.023	-0.022	0.020	0.026	-0.001	0.004	0.001	0.008	0.012	0.216	0.293	0.000	0.000	0.000	0.000
GHQ (1-3)	0.030	-0.021	0.015	-0.003	0.006	-0.022	0.013	0.015	0.004	0.006	-0.014	0.007	0.011	-0.025	0.010	0.362	0.000	0.000	0.000
GHQ (4+worse)	0.045	-0.085	0.003	-0.015	0.021	-0.032	0.029	0.037	0.032	0.016	0.020	0.030	0.023	-0.036	0.008	0.113	0.371	0.000	0.000
Constant	-0.698	-0.087	-0.186	-0.162	-0.113	-0.091	-0.149	-0.165	-0.101	-0.176	-0.066	-0.091	-0.071	-0.236	-0.160	-0.117	-0.083	0.210	0.000
Gamma	0.008	0.001	-0.002	0.004	0.003	-0.001	-0.003	-0.006	-0.002	0.000	0.001	0.001	-0.001	0.008	0.003	0.000	0.001	-0.025	0.024

Male – 8. cause specific hazard model of first event as non-alcohol related death

Cholesky decomposition

	age	AUDIT	Binge	CVD	DM	Cigarettes /day	Phys. actv. (Low)	Phys. actv. (Med)	Phys. actv. (High)	SIMD (2)	SIMD (3)	SIMD (4)	SIMD (Least Deprived)	Other Hos LastYr	Other Hos Over LastYr	GHQ (1-3)	GHQ (4+worse)	Constant	Gamma
age	0.007	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
AUDIT	0.004	0.023	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Binge	0.012	-0.162	0.177	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CVD	-0.040	0.009	0.006	0.172	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
DM	0.015	0.009	0.007	-0.058	0.228	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Cigarettes /day	0.000	-0.001	-0.001	0.000	0.000	0.004	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Low)	0.032	-0.007	-0.021	0.011	0.009	0.015	0.253	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Med)	0.043	-0.009	-0.010	0.030	0.019	0.012	0.059	0.177	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (High)	0.069	-0.015	-0.020	0.035	0.020	0.017	0.058	0.071	0.226	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(2)	-0.012	0.001	0.010	-0.006	0.001	0.005	-0.001	-0.014	-0.005	0.228	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(3)	-0.011	0.000	0.017	-0.001	0.007	-0.015	0.002	-0.010	-0.007	0.106	0.197	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(4)	-0.014	0.001	0.013	-0.005	0.005	0.018	0.001	-0.010	-0.014	0.106	0.067	0.189	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD (Least Deprived)	-0.016	-0.016	0.009	0.000	0.010	0.020	-0.004	-0.019	-0.014	0.106	0.067	0.047	0.216	0.000	0.000	0.000	0.000	0.000	0.000
OtherHos LastYr	-0.020	0.007	0.016	-0.029	-0.014	0.011	0.018	0.030	0.022	-0.011	-0.006	0.009	0.005	0.281	0.000	0.000	0.000	0.000	0.000
OtherHos Over LastYr	-0.015	0.006	0.005	-0.017	-0.012	-0.005	0.013	0.021	0.014	-0.004	0.000	0.005	0.002	0.142	0.163	0.000	0.000	0.000	0.000
GHQ (1-3)	0.012	-0.001	0.006	-0.002	0.000	-0.036	0.012	0.011	0.009	0.005	-0.009	0.006	0.007	-0.018	0.008	0.191	0.000	0.000	0.000
GHQ (4+worse)	0.035	-0.015	0.009	-0.006	0.001	-0.014	0.017	0.022	0.016	0.008	0.017	0.015	0.012	-0.022	0.006	0.052	0.196	0.000	0.000
Constant	-0.508	-0.069	-0.053	-0.106	-0.041	-0.021	-0.063	-0.062	-0.037	-0.104	-0.068	-0.057	-0.035	-0.152	-0.125	-0.056	-0.038	0.104	0.000
Gamma	0.007	0.000	-0.001	0.003	0.002	-0.002	-0.002	-0.004	-0.001	0.000	0.000	0.001	0.000	0.005	0.002	0.001	0.000	-0.014	0.014

Female – 1. cause specific hazard model of first hospitalisation with wholly alcohol-attributable conditions
Cholesky decomposition

	age	AUDIT	Binge	CVD	DM	Cigarettes /day	Phys. actv. (Low)	Phys. actv. (Med)	Phys. actv. (High)	SIMD (2)	SIMD (3)	SIMD (4)	SIMD (Least Deprived)	Other Hos LastYr	OtherHos OverLastYr	GHQ (1-3)	GHQ (4+ worse)	Constant	Gamma
age	0.012	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
AUDIT	0.006	0.035	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Binge	0.027	-0.283	0.364	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CVD	-0.128	0.023	0.020	0.359	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
DM	-0.030	0.014	0.027	-0.195	1.023	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Cigarettes /day	0.000	-0.002	-0.002	0.000	0.000	0.013	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Low)	0.076	-0.009	-0.023	0.033	0.025	-0.006	0.665	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Med)	0.089	-0.001	-0.029	0.058	0.035	-0.020	0.164	0.402	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (High)	0.123	-0.004	-0.056	0.070	0.044	0.026	0.164	0.208	0.361	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(2)	-0.018	-0.006	0.006	0.001	0.003	0.045	-0.014	-0.018	-0.009	0.465	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(3)	-0.036	-0.006	0.001	0.006	0.003	0.045	-0.023	-0.018	-0.018	0.158	0.401	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(4)	-0.049	-0.018	0.002	0.006	0.007	0.090	-0.018	-0.022	-0.036	0.159	0.125	0.534	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD (Least Deprived)	-0.042	0.003	-0.007	0.017	0.005	0.093	-0.025	-0.028	-0.033	0.159	0.125	0.066	0.530	0.000	0.000	0.000	0.000	0.000	0.000
OtherHos LastYr	-0.014	0.010	0.017	-0.038	-0.021	-0.015	0.031	0.043	0.026	0.015	0.022	0.018	0.020	0.567	0.000	0.000	0.000	0.000	0.000
OtherHos OverLastYr	-0.024	-0.012	-0.015	-0.027	-0.010	-0.010	0.023	0.023	0.018	0.010	0.018	0.017	0.025	0.209	0.339	0.000	0.000	0.000	0.000
GHQ (1-3)	0.024	-0.002	0.017	-0.010	0.002	-0.012	0.012	0.021	0.008	0.014	0.014	0.017	0.008	-0.019	-0.003	0.431	0.000	0.000	0.000
GHQ (4+worse)	0.038	-0.042	0.005	-0.013	0.000	-0.071	0.021	0.034	0.027	0.025	0.038	0.019	0.012	-0.042	-0.016	0.143	0.346	0.000	0.000
Constant	-0.584	-0.065	-0.089	-0.152	-0.059	-0.129	-0.168	-0.204	-0.122	-0.171	-0.154	-0.085	-0.077	-0.211	-0.225	-0.147	-0.130	0.230	0.000
Gamma	0.005	0.001	0.003	0.003	0.002	-0.001	-0.003	-0.007	0.000	-0.001	0.000	0.000	-0.001	0.006	0.005	0.000	0.002	-0.031	0.031

Female – 2. cause specific hazard model of first hospitalisation with partly alcohol-attributable conditions
Cholesky decomposition

	age	AUDIT	Binge	CVD	DM	Cigarettes /day	Phys. actv. (Low)	Phys. actv. (Med)	Phys. actv. (High)	SIMD (2)	SIMD (3)	SIMD (4)	SIMD (Least Deprived)	Other Hos LastYr	OtherHos Over LastYr	GHQ (1-3)	GHQ (4+ worse)	Constant	Gamma
age	0.003	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
AUDIT	0.004	0.016	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Binge	0.001	-0.092	0.105	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CVD	-0.031	0.005	0.007	0.093	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
DM	0.002	0.007	0.006	-0.047	0.220	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Cigarettes /day	0.000	0.000	0.000	0.000	0.000	0.005	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Low)	0.019	-0.007	-0.006	0.011	0.007	-0.003	0.145	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Med)	0.026	-0.009	-0.008	0.018	0.011	-0.007	0.060	0.097	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (High)	0.035	-0.015	-0.015	0.022	0.013	0.001	0.060	0.055	0.104	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(2)	-0.005	-0.004	0.001	0.001	0.001	0.009	-0.004	-0.003	-0.001	0.131	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(3)	-0.007	-0.007	-0.001	0.002	0.002	0.012	-0.004	-0.003	-0.004	0.062	0.111	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(4)	-0.008	-0.007	0.000	0.004	0.003	0.021	-0.005	-0.004	-0.006	0.062	0.039	0.112	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD (Least Deprived)	-0.007	-0.007	-0.004	0.007	0.004	0.022	-0.007	-0.005	-0.006	0.062	0.039	0.025	0.106	0.000	0.000	0.000	0.000	0.000	0.000
OtherHos LastYr	-0.005	0.003	0.003	-0.012	-0.006	0.002	0.008	0.012	0.007	0.001	0.004	0.003	0.003	0.149	0.000	0.000	0.000	0.000	0.000
OtherHos OverLastYr	-0.004	0.001	-0.002	-0.008	-0.004	0.002	0.005	0.006	0.005	0.001	0.004	0.003	0.003	0.045	0.086	0.000	0.000	0.000	0.000
GHQ (1-3)	0.006	0.002	0.002	-0.004	0.000	-0.002	0.006	0.006	0.002	0.005	0.005	0.005	0.002	-0.006	-0.002	0.101	0.000	0.000	0.000
GHQ (4+worse)	0.012	-0.008	0.001	-0.003	-0.002	-0.014	0.007	0.008	0.003	0.005	0.009	0.005	0.002	-0.011	-0.002	0.032	0.111	0.000	0.000
Constant	-0.194	-0.023	-0.018	-0.047	-0.019	-0.028	-0.058	-0.051	-0.022	-0.063	-0.045	-0.029	-0.023	-0.047	-0.057	-0.033	-0.020	0.060	0.000
age	0.002	0.000	0.001	0.001	0.001	-0.001	-0.001	-0.002	0.000	0.000	0.000	0.000	0.000	0.002	0.001	0.000	0.000	-0.007	0.007

Female – 3. cause specific hazard model of first hospitalisation with non-emergency& non-CVD conditions
Cholesky decomposition

	age	AUDIT	Binge	BMI (over weight)	BMI (obesity)	CVD	DM	Cigarettes/ day	Phys. actv. (Low)	Phys. actv. (Med)	Phys. actv. (High)	SIMD (2)	SIMD (3)	SIMD (4)	SIMD (Least Deprived)	OtherHos Last Yr	Other Hos Over LastYr	GHQ (1-3)	GHQ (4+ worse)	Constant	Gamma
age	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
AUDIT	0.001	0.004	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Binge	-0.001	-0.025	0.028	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
BMI (over weight)	-0.003	0.000	0.000	0.028	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
BMI (obesity)	-0.003	0.000	0.000	0.015	0.030	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CVD	-0.009	0.002	0.002	-0.002	-0.004	0.027	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
DM	0.000	0.002	0.002	-0.002	-0.005	-0.015	0.063	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Cigarettes /day	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Low)	0.005	-0.002	-0.002	0.000	0.002	0.003	0.002	-0.001	0.045	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Med)	0.007	-0.002	-0.002	0.000	0.003	0.005	0.004	-0.002	0.020	0.029	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (High)	0.009	-0.003	-0.004	0.002	0.005	0.006	0.004	0.000	0.020	0.018	0.026	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(2)	-0.002	-0.001	0.000	0.000	0.001	0.000	0.000	0.003	-0.001	-0.001	0.000	0.035	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(3)	-0.002	-0.002	-0.001	0.000	0.001	0.000	0.000	0.004	-0.001	-0.001	-0.001	0.017	0.031	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(4)	-0.003	-0.002	0.000	0.000	0.002	0.001	0.001	0.006	-0.001	-0.001	-0.001	0.017	0.010	0.030	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD (Least Deprived)	-0.003	-0.002	-0.001	0.001	0.003	0.001	0.001	0.006	-0.002	-0.001	-0.002	0.017	0.010	0.007	0.032	0.000	0.000	0.000	0.000	0.000	0.000
OtherHos LastYr	-0.002	0.001	0.001	0.000	0.000	-0.003	-0.002	0.000	0.002	0.003	0.002	0.000	0.001	0.001	0.001	0.038	0.000	0.000	0.000	0.000	0.000
OtherHos OverLastYr	-0.001	0.000	-0.001	0.000	-0.001	-0.002	-0.001	0.000	0.001	0.001	0.001	0.000	0.001	0.001	0.001	0.016	0.024	0.000	0.000	0.000	0.000
GHQ (1-3)	0.002	0.000	0.000	0.000	0.000	-0.001	0.000	-0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.000	-0.001	0.000	0.028	0.000	0.000	0.000
GHQ (4+worse)	0.003	-0.002	0.001	0.000	0.000	-0.001	0.000	-0.004	0.002	0.002	0.001	0.001	0.002	0.001	0.000	-0.003	0.000	0.009	0.030	0.000	0.000
Constant	-0.047	-0.007	-0.005	-0.014	-0.012	-0.012	-0.006	-0.007	-0.020	-0.018	-0.008	-0.018	-0.012	-0.008	-0.006	-0.016	-0.015	-0.009	-0.006	0.016	0.000
Gamma	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	-0.002	0.002

Female – 4. cause specific hazard model of first hospitalisation with non-emergency& CVD conditions
Cholesky decomposition

	age	AUDIT	Binge	BMI (over weight)	BMI (obesity)	CVD	DM	Cigarettes /day	Phys. actv. (Low)	Phys. actv. (Med)	Phys. actv. High)	SIMD (2)	SIMD (3)	SIMD (4)	SIMD (Least Deprived)	Other Hos LastYr	OtherHos OverLastYr	GHQ (1-3)	GHQ (4+worse)	Constant	Gamma
age	0.007	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
AUDIT	0.009	0.039	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Binge	0.008	-0.207	0.206	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
BMI (over weight)	-0.013	-0.010	0.000	0.231	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
BMI (obesity)	-0.001	-0.011	-0.003	0.168	0.195	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CVD	-0.055	0.007	0.017	-0.013	-0.020	0.188	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
DM	0.006	0.015	0.016	-0.014	-0.028	-0.051	0.257	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Cigarettes /day	0.002	-0.001	-0.001	0.000	0.001	0.001	0.000	0.009	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Low)	0.036	-0.012	-0.015	-0.006	0.013	0.014	0.011	0.005	0.266	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Med)	0.059	-0.022	-0.022	0.002	0.021	0.027	0.025	-0.011	0.097	0.188	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (High)	0.078	-0.034	-0.037	0.013	0.030	0.037	0.029	0.003	0.098	0.094	0.215	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(2)	-0.007	-0.008	0.001	0.004	0.010	0.002	0.005	0.024	-0.002	-0.006	-0.002	0.236	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(3)	-0.010	-0.018	-0.003	-0.003	0.007	0.002	0.009	0.030	-0.004	-0.008	-0.010	0.134	0.240	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(4)	-0.009	-0.017	-0.002	0.001	0.015	0.005	0.013	0.044	-0.006	-0.009	-0.012	0.134	0.059	0.252	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD (Least Deprived)	-0.009	-0.020	-0.012	0.009	0.020	0.012	0.015	0.042	-0.010	-0.013	-0.013	0.134	0.059	0.042	0.196	0.000	0.000	0.000	0.000	0.000	0.000
OtherHos LastYr	-0.007	0.007	0.005	-0.002	0.001	-0.024	-0.015	0.013	0.012	0.027	0.021	0.000	0.006	0.009	0.011	0.270	0.000	0.000	0.000	0.000	0.000
OtherHos Over LastYr	-0.008	0.004	-0.004	-0.006	-0.003	-0.019	-0.012	0.007	0.009	0.015	0.016	0.003	0.005	0.007	0.006	0.128	0.169	0.000	0.000	0.000	0.000
GHQ (1-3)	0.007	0.003	0.005	-0.002	-0.002	-0.007	0.003	0.000	0.014	0.019	0.008	0.010	0.011	0.009	0.003	-0.015	-0.004	0.218	0.000	0.000	0.000
GHQ (4+worse)	0.027	-0.011	0.005	0.003	-0.006	-0.004	-0.008	-0.028	0.016	0.017	0.010	0.008	0.018	0.010	0.009	-0.024	0.002	0.053	0.208	0.000	0.000
Constant	-0.476	-0.032	-0.038	-0.155	-0.070	-0.138	-0.050	-0.062	-0.099	-0.090	-0.048	-0.137	-0.069	-0.052	-0.052	-0.134	-0.109	-0.056	-0.043	0.113	0.000
Gamma	0.006	-0.001	0.001	0.001	0.000	0.002	0.002	-0.002	-0.002	-0.004	-0.001	-0.001	0.000	0.000	0.000	0.005	0.002	0.001	0.001	-0.018	0.019

Female – 5. cause specific hazard model of first hospitalisation with emergency & Non-CVD conditions
Cholesky decomposition

	age	AUDIT	Binge	BMI (over weight)	BMI (obesity)	CVD	DM	Cigarettes /day	Phys. actv. (Low)	Phys. actv. (Med)	Phys. actv. (High)	SIMD (2)	SIMD (3)	SIMD (4)	SIMD (Least Deprived)	Other Hos LastYr	Other Hos Over LastYr	GHQ (1-3)	GHQ (4+worse)	Constant	Gamma
age	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
AUDIT	0.001	0.006	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Binge	0.000	-0.035	0.040	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
BMI (over weight)	-0.005	-0.001	0.000	0.044	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
BMI (obesity)	-0.003	0.001	0.001	0.020	0.039	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CVD	-0.013	0.002	0.003	-0.003	-0.006	0.036	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
DM	0.000	0.002	0.002	-0.002	-0.006	-0.018	0.070	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Cigarettes /day	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.002	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Low)	0.007	-0.002	-0.002	0.000	0.003	0.004	0.003	-0.001	0.057	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Med)	0.009	-0.003	-0.003	0.000	0.005	0.007	0.005	-0.003	0.018	0.038	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (High)	0.013	-0.004	-0.006	0.002	0.007	0.009	0.006	0.000	0.018	0.019	0.039	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(2)	-0.002	-0.001	0.000	0.000	0.002	0.000	0.000	0.003	-0.001	-0.001	-0.001	0.046	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(3)	-0.003	-0.003	-0.001	-0.001	0.001	0.001	0.000	0.005	-0.002	-0.001	-0.002	0.020	0.044	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(4)	-0.003	-0.002	0.000	0.000	0.003	0.001	0.001	0.008	-0.002	-0.002	-0.002	0.020	0.012	0.044	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD (Least Deprived)	-0.003	-0.002	-0.001	0.000	0.004	0.002	0.001	0.008	-0.003	-0.002	-0.003	0.020	0.012	0.009	0.047	0.000	0.000	0.000	0.000	0.000	0.000
OtherHos LastYr	-0.002	0.001	0.001	0.000	-0.001	-0.005	-0.003	0.000	0.003	0.005	0.003	0.001	0.001	0.002	0.001	0.053	0.000	0.000	0.000	0.000	0.000
OtherHos Over LastYr	-0.002	0.000	-0.001	0.000	-0.001	-0.003	-0.001	0.000	0.002	0.003	0.002	0.001	0.001	0.002	0.002	0.023	0.033	0.000	0.000	0.000	0.000
GHQ (1-3)	0.002	0.001	0.000	0.000	0.000	-0.002	0.000	-0.001	0.002	0.003	0.001	0.002	0.002	0.002	0.001	-0.002	0.000	0.039	0.000	0.000	0.000
GHQ (4+worse)	0.004	-0.003	0.000	0.001	0.000	-0.001	-0.001	-0.005	0.003	0.004	0.002	0.002	0.003	0.002	0.001	-0.005	0.000	0.014	0.041	0.000	0.000
Constant	-0.065	-0.009	-0.007	-0.020	-0.016	-0.018	-0.008	-0.010	-0.018	-0.019	-0.010	-0.021	-0.014	-0.011	-0.008	-0.024	-0.022	-0.014	-0.009	0.023	0.000
Gamma	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	-0.001	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.000	0.000	-0.003	0.003

Female – 6. cause specific hazard model of first hospitalisation with emergency & CVD conditions

Cholesky decomposition

	age	AUDIT	Binge	BMI (over weight)	BMI (obesity)	CVD	DM	Cigarettes /day	Phys. actv. (Low)	Phys. actv. (Med)	Phys. actv. (High)	SIMD (2)	SIMD (3)	SIMD (4)	SIMD (Least Deprived)	Other Hos LastYr	Other Hos Over LastYr	GHQ (1-3)	GHQ (4+worse)	Constant	Gamma
age	0.005	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
AUDIT	0.006	0.029	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Binge	0.005	-0.147	0.177	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
BMI (over weight)	-0.004	-0.001	0.002	0.140	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
BMI (obesity)	0.005	0.000	0.002	0.098	0.128	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CVD	-0.030	0.004	0.008	-0.008	-0.014	0.122	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
DM	0.007	0.009	0.005	-0.011	-0.016	-0.041	0.165	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Cigarettes /day	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.005	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Low)	0.025	-0.011	-0.007	-0.005	0.008	0.009	0.006	0.001	0.180	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Med)	0.040	-0.015	-0.010	-0.001	0.012	0.018	0.015	-0.010	0.050	0.126	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (High)	0.051	-0.023	-0.018	0.005	0.020	0.023	0.018	0.002	0.050	0.059	0.154	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(2)	-0.005	-0.005	0.000	0.003	0.008	0.004	0.002	0.015	-0.002	-0.002	-0.001	0.164	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(3)	-0.007	-0.009	-0.001	-0.001	0.004	0.005	0.008	0.015	-0.003	-0.004	-0.007	0.071	0.140	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(4)	-0.005	-0.010	-0.001	0.001	0.009	0.006	0.009	0.027	-0.003	-0.005	-0.008	0.071	0.049	0.138	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD (Least Deprived)	-0.004	-0.013	-0.007	0.006	0.012	0.009	0.009	0.026	-0.005	-0.007	-0.008	0.071	0.049	0.032	0.165	0.000	0.000	0.000	0.000	0.000	0.000
OtherHos LastYr	-0.005	0.006	0.004	0.000	-0.002	-0.016	-0.011	0.003	0.009	0.021	0.015	-0.001	0.001	0.008	0.005	0.172	0.000	0.000	0.000	0.000	0.000
OtherHos Over LastYr	-0.002	0.002	-0.002	-0.005	-0.003	-0.012	-0.010	0.006	0.007	0.013	0.011	0.001	0.005	0.006	0.002	0.069	0.110	0.000	0.000	0.000	0.000
GHQ (1-3)	0.006	0.006	0.004	0.007	-0.002	-0.007	0.002	-0.002	0.010	0.009	0.007	0.007	0.009	0.009	0.001	-0.014	-0.003	0.140	0.000	0.000	0.000
GHQ (4+worse)	0.019	0.000	0.003	0.002	0.000	-0.005	-0.005	-0.020	0.012	0.015	0.008	0.007	0.016	0.008	0.004	-0.020	-0.003	0.041	0.135	0.000	0.000
Constant	-0.354	-0.030	-0.019	-0.089	-0.043	-0.080	-0.032	-0.035	-0.050	-0.053	-0.028	-0.073	-0.057	-0.041	-0.023	-0.072	-0.066	-0.044	-0.034	0.075	0.000
Gamma	0.004	-0.001	0.001	0.000	0.000	0.002	0.001	-0.002	-0.001	-0.003	-0.001	0.000	0.000	0.000	0.000	0.003	0.002	0.001	0.001	-0.010	0.010

Female – 7. cause specific hazard model of first event as alcohol-related death

Cholesky decomposition

	age	AUDIT	Binge	CVD	DM	Cigarettes /day	Phys. actv. (Low)	Phys. actv. (Med)	Phys. actv. (High)	SIMD (2)	SIMD (3)	SIMD (4)	SIMD (Least Deprived)	Other Hos LastYr	Other Hos Over LastYr	GHQ (1-3)	GHQ (4+worse)	Constant	Gamma
age	0.012	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
AUDIT	0.007	0.041	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Binge	0.047	-0.314	0.369	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CVD	-0.092	0.014	0.021	0.328	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
DM	0.016	0.025	0.029	-0.148	0.733	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Cigarettes /day	0.002	-0.002	-0.001	0.001	0.000	0.013	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Low)	0.071	-0.006	-0.020	0.035	0.016	-0.009	0.556	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Med)	0.101	-0.003	-0.033	0.062	0.029	-0.035	0.113	0.339	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (High)	0.143	-0.021	-0.061	0.080	0.035	0.001	0.111	0.159	0.527	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(2)	-0.017	0.008	0.016	0.009	0.006	0.035	-0.011	-0.011	-0.004	0.430	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(3)	-0.026	-0.005	-0.001	0.011	0.013	0.035	-0.012	-0.013	-0.009	0.239	0.398	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(4)	-0.022	-0.009	0.004	0.014	0.013	0.084	-0.015	-0.021	-0.018	0.239	0.119	0.448	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD (Least Deprived)	-0.021	0.004	-0.006	0.026	0.017	0.084	-0.021	-0.024	-0.020	0.239	0.118	0.074	0.413	0.000	0.000	0.000	0.000	0.000	0.000
OtherHos LastYr	-0.014	0.019	0.014	-0.041	-0.019	0.003	0.026	0.037	0.022	0.001	0.005	0.015	0.013	0.600	0.000	0.000	0.000	0.000	0.000
OtherHos Over LastYr	-0.010	-0.006	-0.011	-0.031	-0.006	0.017	0.017	0.021	0.016	0.002	0.013	0.015	0.019	0.354	0.340	0.000	0.000	0.000	0.000
GHQ (1-3)	0.014	0.015	0.018	-0.018	0.002	-0.016	0.021	0.030	0.012	0.024	0.017	0.022	0.008	-0.032	0.009	0.377	0.000	0.000	0.000
GHQ (4+worse)	0.036	-0.045	-0.001	-0.002	-0.009	-0.077	0.022	0.036	0.018	0.034	0.040	0.024	0.017	-0.040	-0.001	0.112	0.375	0.000	0.000
Constant	-0.801	-0.073	-0.076	-0.181	-0.062	-0.105	-0.102	-0.122	-0.055	-0.246	-0.142	-0.097	-0.083	-0.366	-0.262	-0.113	-0.080	0.219	0.000
Gamma	0.010	0.001	0.002	0.004	0.002	-0.003	-0.004	-0.010	-0.001	-0.001	0.001	0.000	-0.001	0.006	0.003	0.001	0.000	-0.025	0.024

Female – 8. cause specific hazard model of first event as non-alcohol related death

Cholesky decomposition

	age	AUDIT	Binge	CVD	DM	Cigarettes /day	Phys. actv. (Low)	Phys. actv. (Med)	Phys. actv. (High)	SIMD (2)	SIMD (3)	SIMD (4)	SIMD (Least Deprived)	Other Hos LastYr	Other Hos Over LastYr	GHQ (1-3)	GHQ (4+worse)	Constant	Gamma
age	0.008	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
AUDIT	0.009	0.045	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Binge	0.009	-0.262	0.331	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CVD	-0.027	0.002	0.008	0.182	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
DM	0.017	0.014	0.007	-0.063	0.257	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Cigarettes /day	0.002	-0.001	0.000	0.001	0.000	0.007	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Low)	0.041	-0.013	-0.012	0.011	0.004	-0.003	0.302	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (Med)	0.064	-0.024	-0.014	0.027	0.016	-0.022	0.054	0.192	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Phys. actv. (High)	0.083	-0.040	-0.021	0.031	0.020	0.000	0.053	0.084	0.331	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(2)	-0.010	-0.007	0.001	0.009	0.006	0.018	-0.002	-0.002	-0.002	0.222	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(3)	-0.014	-0.013	-0.001	0.011	0.014	0.013	-0.003	-0.009	-0.008	0.110	0.218	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD(4)	-0.007	-0.019	-0.003	0.010	0.012	0.038	-0.004	-0.010	-0.009	0.110	0.059	0.205	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SIMD (Least Deprived)	-0.013	-0.019	-0.009	0.013	0.014	0.036	-0.006	-0.008	-0.009	0.109	0.058	0.046	0.313	0.000	0.000	0.000	0.000	0.000	0.000
OtherHos LastYr	-0.009	0.016	0.008	-0.022	-0.014	-0.006	0.014	0.029	0.021	-0.008	-0.006	0.014	0.007	0.296	0.000	0.000	0.000	0.000	0.000
OtherHos Over LastYr	0.001	0.005	-0.003	-0.019	-0.012	0.012	0.008	0.021	0.017	-0.004	0.006	0.011	0.003	0.137	0.175	0.000	0.000	0.000	0.000
GHQ (1-3)	0.003	-0.002	0.007	-0.014	0.005	-0.004	0.011	0.016	0.008	0.014	0.015	0.020	0.001	-0.022	-0.001	0.199	0.000	0.000	0.000
GHQ (4+worse)	0.022	-0.014	-0.003	-0.006	-0.010	-0.035	0.014	0.023	0.010	0.011	0.021	0.013	0.007	-0.027	-0.004	0.061	0.229	0.000	0.000
Constant	-0.647	-0.040	-0.020	-0.115	-0.042	-0.042	-0.048	-0.061	-0.032	-0.108	-0.067	-0.064	-0.027	-0.143	-0.129	-0.073	-0.042	0.113	0.000
Gamma	0.007	-0.001	0.001	0.002	0.002	-0.003	-0.002	-0.007	-0.001	-0.001	0.000	0.000	0.000	0.005	0.003	0.001	0.001	-0.014	0.015

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