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Exploring the importance of links between health behaviours for economic evaluations of behaviour-change strategies: A case study considering the link between smoking cigarettes and drinking alcohol

A thesis submitted for the degree of Doctor of Philosophy

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Glossary

AAF	Alcohol-attributable fraction
ABS	Australian Bureau of Statistics
AIC	Akaike information criterion
ALD	Alcoholic liver disease
ALSPAC	Avon Longitudinal Study of Parents and Children
AOCM	All other cause mortality
APE	Average partial effect
AR	At-risk drinking
ARD	Alcohol-related disease
BENESCO	Benefits of Smoking Cessation on Outcomes
BHPS	British Household Panel Survey
BIC	Bayesian information criterion
BIT	Behavioural Interactions in Tobacco use
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CHD	Coronary heart disease
CI	Confidence interval
CMA	Cost-minimisation analysis
COPD	Chronic obstructive pulmonary disease
CPI	Consumer Price Index
CrI	Credible intervals
CUA	Cost-utility analysis
DALY	Disability-Adjusted Life Year
DES	Discrete event simulation
DR	Annual discount rate
Dri	Instantaneous discount rate
DSM	Diagnostic and Statistical Manual of Mental Disorders
ELSA	English Longitudinal Study of Ageing
EVPI	Expected value of perfect information
FACS	Families and Children Study
GHS	General Household Survey
GLS	General Lifestyle Survey
GP	General Practitioner
HECOS	Health and Economic Consequences of Smoking
HES	Hospital Episode Statistics
HILDA	The Household, Income and Labour Dynamics in Australia survey
HMIC	Health Management Information Consortium
HODaR	Health Outcomes Data Repository
HRQoL	Health-related quality of life
HRS	Health and Retirement Survey
HSE	Health Survey for England
HTA	Health Technology Assessment
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio

IIA	Independence from irrelevant alternatives
INB	Incremental net benefit
ITC-4	The International Tobacco Control Four Country Survey
LCS	Living Cost and Food Survey
LY	Life year
ML	Maximum likelihood
MSL	Maximum simulated likelihood
MVP	Multivariate probit
NAR	Not at-risk drinking
NB	Net benefit
NDSHS	National Drug Strategy Household Survey
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NRT	Nicotine Replacement Therapy
NS	Non-smoking
NWPHO	North West Public Health Observatory
ONS	Office for National Statistics
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSID	Panel Study of Income Dynamics
PSS	Personal Social Services
QALY	Quality Adjusted Life Year
RCT	Randomised controlled trial
RR	Relative risk
S	Smoking
SAPM	Sheffield Alcohol Policy Model
SARG	Sheffield Alcohol Research Group
SDD	Smoking, Drinking and Drugs Use among Young People
SOEP	Socio-Economic Panel Study
SRD	Smoking-related disease
SRDMC	Smoking-related disease medical costs
STA	Single Technology Appraisal
STOP	Smoking Cessation Treatment and Outcomes Patterns
TARN	Trauma Audit and Research Network
TOLE	Time of last event
TONE	Time of next event
UK	United Kingdom
US	United States of America
VL	Visual Logic
WHO	World Health Organization

Abstract

Links between health behaviours are potentially of great importance for cost-effectiveness estimates in economic evaluations of behaviour change strategies. This thesis investigates bias in economic evaluations due to the omission of links between health behaviours. A framework to evaluate the health costs and consequences of behaviour change strategies while accounting for links to other health-related behaviours is proposed, and tested using a case study of the link between tobacco and alcohol use.

There is strong evidence of correlation between alcohol use and tobacco use. Nevertheless, while many economic evaluations of interventions for alcohol and tobacco behaviour change have been conducted and used to inform resource allocation decisions, none have considered implications of links between the two behaviours. Assumptions about behaviour beyond typical trial endpoints in historical economic evaluations have in general been based on limited follow-up data. Analysis of the joint dynamics of tobacco and alcohol use employing large-scale longitudinal survey data is used in this thesis as an alternative to inform assumptions about long-run smoking behaviour and its link to alcohol use, in a *de novo* individual-level simulation to appraise the cost-effectiveness of smoking cessation interventions.

Smoking behaviour is found to be persistent and dynamically linked to alcohol use, but also influenced by numerous other factors, including unobserved time-invariant person-specific characteristics which determine the propensity to smoke. The ability of smoking cessation interventions to permanently reduce the propensity to smoke is important for their long-run cost-effectiveness. In the absence of data on this effect, historical economic evaluations may have misinformed decision makers. There is a need for robust and tested assumptions about long-term behaviour and case by case consideration of the importance of inter-behavioural links in future economic evaluations of behaviour change strategies, and for further investigation into the dynamics and interrelation of health-related behaviours.

1. Chapter 1: Introduction

Links between health behaviours are potentially of great importance for cost-effectiveness estimates in economic evaluations of competing behaviour change strategies. The aim of this thesis is to investigate bias in health economic evaluations of behaviour change strategies caused by omission of links between different behaviours. A framework proposed to evaluate the health costs and consequences of behaviour change strategies while accounting for links to other health-related behaviours is set out, and tested using a case study of the link between alcohol use and smoking.

In this chapter, the concept of health-related behaviour is introduced, the use of economic evaluation methods to justify healthcare resource allocation decisions described, and a framework to conduct economic evaluations of health-related behaviours proposed.

1.1. Health-related Behaviour

Health-related behaviours are defined as the behaviours or habits of individuals that directly impact health (be it own-health or the health of others), as supported by evidence. For brevity, the term 'health-related behaviour' is used interchangeably with 'health behaviour' throughout this thesis. Examples of health behaviours include smoking tobacco, drinking excessive amounts of alcohol, exercising, diet choices and taking care of sexual and mental wellbeing [1, 2]. Factors that influence health but cannot be attributed to behaviour, such as age and gender, are not health behaviours, nor are behaviours for which there is no evidence that they are linked to health, for which there is evidence that the link to health is negligible, nor for which there is substantiated evidence that there is no link to health.

If people in the UK didn't smoke, drink alcohol to excess, ate more healthily, and improved other health-related behaviours, the financial burden of health-related diseases upon the National Health Service (NHS) would be significantly reduced [1, 3]. In recognition of this, public resources are committed to improving health behaviours through a variety of measures. To cite two examples, public funds have been dedicated to policies inside and outside of schools to improve the diet choices

of UK children in recent years [4], while the NHS Stop Smoking service has been in operation since the turn of the century [5]. When there is a choice between funding competing alternatives to improve health behaviours in the context of a finite public budget, the choice between alternatives is of consequence to the public purse and public health. This raises the question of how healthcare financing decisions are made in the UK.

1.2. Economic Evaluation to Justify Healthcare Resource Allocation Decisions

1.2.1. Health Economic Methods for Health Technology Appraisal

Since 1999, the National Institute for Health and Care Excellence (NICE) has been mandated by the Department of Health to appraise the health benefits and costs of new and established health technologies in England and Wales [6]. Economic evaluation involves the examination of both costs and consequences of two or more alternatives [7] and is the preferred means of appraisal in England and Wales [6].

The value of each alternative A_i considered in an economic evaluation can be expressed as its net benefit (NB) [8]:

$$NB(A_i) = e_i\lambda - c_i \quad i = 1,2,..,n \tag{1}$$

where e_i denotes the benefits and c_i the total costs of alternative i. In the NICE reference case [9], health benefits are measured in Quality Adjusted Life Years (QALYs), the perspective on costs in health technology appraisal is of the NHS and personal social services (PSS) and the perspective on benefits is of all direct health effects on patients or, where relevant, carers. The symbol λ describes the societal willingness to pay threshold for health benefits, enabling monetary quantification of the NB of each alternative [6]. In the UK, this is around £20,000 to £30,000 per QALY [6].

The relative benefit of one competing alternative *i* over another *j* can then be expressed as incremental net benefit (INB):

$$INB(A_{ij}) = (e_i - e_j)\lambda - (c_i - c_j) \quad i \neq j \tag{2}$$

In this way, the gains or losses of selecting alternative *i* over alternative *j* can be quantified in monetary terms. If $INB(A_{ij})$ is positive, *i* is preferable to *j*.

Alternatively, where the willingness to pay threshold is not fixed, not known, or where decision makers wish to use discretion, the relative merits of alternative *i* over *j* can be assessed using an incremental cost-effectiveness ratio (ICER), which can be compared to different thresholds:

$$ICER(A_{ij}) = {(c_i - c_j)}\Big/{(e_i - e_j)} \quad i \neq j \qquad (3)$$

A robust economic evaluation will compare alternatives with the full range of available alternatives, incorporating all appropriate evidence and reflecting uncertainty in the evidence in the conclusion of the analysis [10]. Health economic models are used to combine data from different sources and often to extrapolate to long-term costs and consequences [10]. Uncertainty in the evidence can be characterised using probabilistic sensitivity analysis (PSA). PSA is conducted by first assigning probability distributions to uncertain input parameters, then sampling from these probability distributions, incorporating correlation where appropriate, to generate an INB estimate multiple times. The distribution of INB estimates describes uncertainty around the INB of one competing alternative versus another, providing the decision maker with information about the probability that treatment *i* has a positive INB, as well as the point estimate of INB. More recently, health economic models have been used to quantify the value of collecting further information to reduce uncertainty around the INB estimate [11].

1.2.2. Economic evaluation for health behaviour interventions

The relative benefits and costs of health technologies have not been appraised equally across all types of healthcare interventions. Public health has been broadly defined as the art and science of preventing disease, prolonging life and promoting health through community efforts [12] and public health measures range from disease vaccination to motor vehicle safety. In contrast, 'clinical' interventions have been more narrowly defined as comprising drugs, devices and medical procedures [13]. These two definitions are clearly not mutually exclusive. In the case of behaviour change interventions, 'clinical' strategies can be used to improve public health, as is the case with Nicotine Replacement Therapy (NRT) for smoking

cessation. Some public health strategies are non-clinical though: a tobacco tax increase could be viewed as a public health strategy if the aim is to reduce smoking. The reason for drawing a distinction between 'public health' interventions and 'clinical' interventions is to highlight that the majority of health technology evaluations have focussed on clinical interventions [12]. Key methodological challenges for economic appraisal of public health interventions have been highlighted, including the attribution of effects, measuring and valuing of outcomes and identification of inter-sector costs and consequences, explaining this trend [13].

Given the different challenges for economic appraisals of clinical and public health interventions, it is as expected that more 'clinical' than 'public health' behaviour change strategies have had supporting economic evidence in England and Wales. However, NICE guidance on smoking cessation and prevention, prevention of harmful drinking, treatment for drug abuse, promotion of physical activity and prevention of obesity and social and emotional wellbeing have all been supported by bespoke economic analyses [9]. NICE is clearly keen to use the same criteria to support decisions between competing alternatives for behaviour change strategies as is used for competing alternatives for clinical disease treatment. These bespoke economic analyses supporting NICE guidance have however not considered links between health behaviours.

1.2.3. Summary

Economic evaluation is a widely used means of deciding between competing strategies to improve health behaviours in England and Wales, and much of the guidance for behaviour change strategies is supported by economic evidence. Guidance for strategies to improve various health behaviours has been supported by bespoke economic analyses, but none of these analyses have considered links to other health behaviours, and the possible consequences [9]. With this in mind, the next section sets out a framework for economic evaluation of health behaviour interventions with the implicit inclusion of inter-behavioural links and their consequences, which this thesis will test.

1.3. A Framework for Economic Evaluation of an Intervention to Improve Health Behaviour

The proposed framework is an extension of the usual steps of an economic modelling study, for the case of competing health behaviour change strategies. The framework is described by the flow diagram, Figure 1.

The assumed starting point for the framework is an answerable research question, such as 'What is the cost-effectiveness of Treatment X in comparison to Treatment Y for smoking cessation in population Z?' It is first important to identify the existing economic evaluations in the area. The type and structure of any economic model used should be determined by the natural pathway of the diseases and clinical and care process at hand [14, 15], and past economic evaluations can inform appropriate model structure and type. In the context of evaluating strategies to change behaviour, a review of existing economic studies would also reveal whether behavioural links have been considered in any analyses to date.

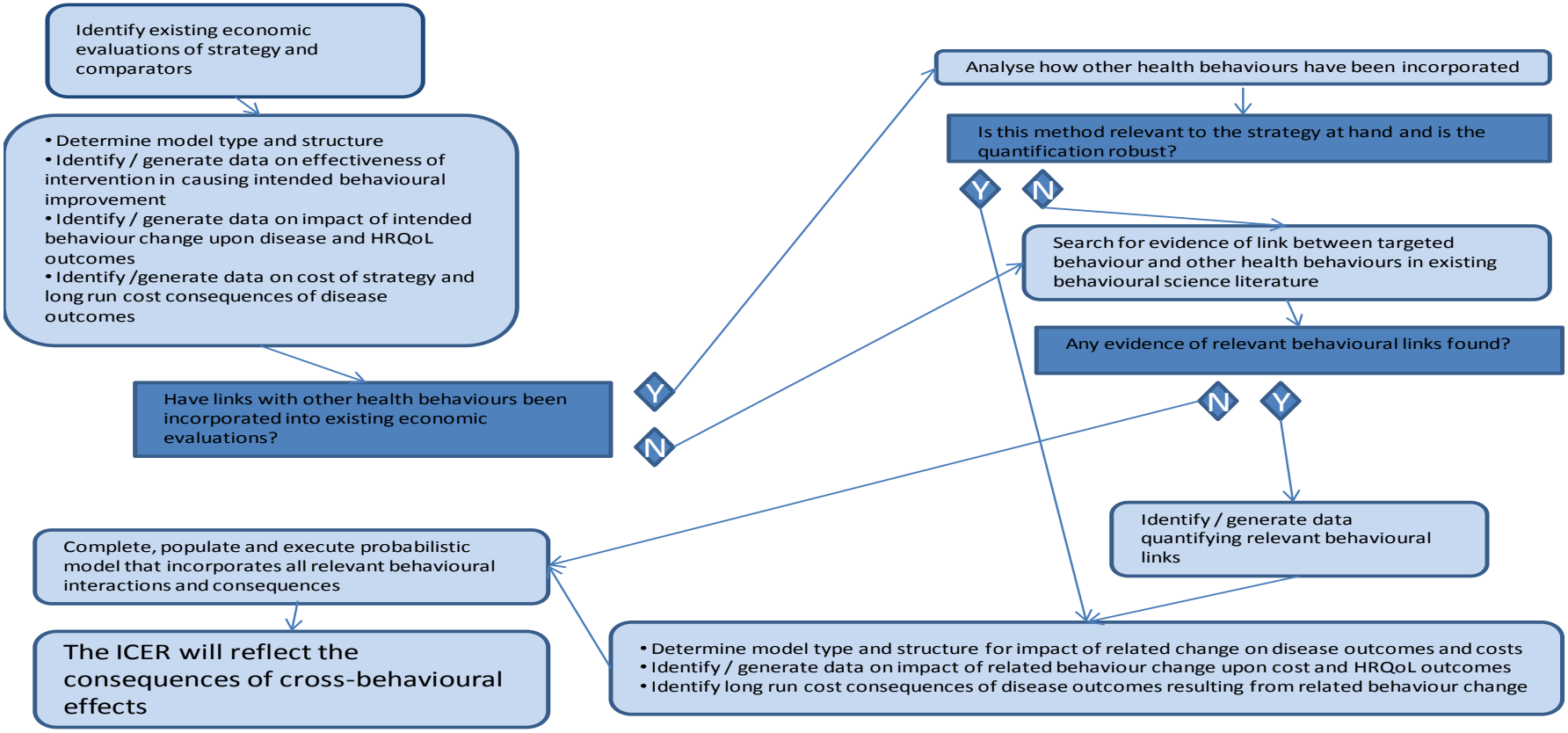
Once the model type and structure had been determined, it would be necessary to source the outcome, cost and probability data for the model. The model should be based on the highest quality data available [16, 17], consistent with the perspective of the analysis and population of interest. Randomised controlled trial (RCT) data are established as the gold standard source of data for decision modelling, though there are limitations to RCT data such as typically short follow-up, and thus retrospective data, observational trials and expert opinion are often needed to answer the research question and are valid data sources [15, 16].

It would then be necessary to understand the effectiveness of the strategy in improving the targeted behaviour, and the impact of behaviour change upon disease outcomes. Past economic analyses would likely yield data fit for this purpose, but it may be necessary to conduct separate searches of effectiveness studies. Past economic evaluations could provide appropriate cost data for the model, inflated where appropriate, but again it may be necessary to conduct a separate search to identify the best available cost data.

Next are the issues specific to interventions to change behaviour. It would be necessary to investigate links between the targeted health behaviour and other

health behaviours, and also what consequences these would have for costs and outcomes.

Figure 1: Flow Diagram Depicting Stages Involved in an Economic Evaluation of Behaviour Change Strategies



If past economic evaluations have incorporated inter-behavioural links into their analyses, it would be necessary to understand how they have quantified such links and the uncertainty surrounding them. Regardless, an explorative search of the behavioural science literature would be beneficial to learn about the potential links the targeted health behaviour has with other health behaviours. Once behavioural links have been identified, quantification of these links would be needed in an appropriate form for incorporation into the economic model. It may be that trial data can be informative here, but retrospective observational data or even expert opinion data may be the best source available.

Next, the cost and disease outcomes of changes in related behaviours would need to be modelled. This would essentially involve developing an adjoining economic model for each related behaviour. Searches for past economic models of behaviour change interventions for the related behaviour(s) would be necessary, and once model type and structure are determined, cost, outcome and probability data would need to be sourced for the model. The remaining tasks would include building and populating the economic model, modelling input uncertainty appropriately to enable PSA and value of further information analysis. The decision maker would then be able to perform their role with the capability that contemporary health economic models offer, with the implicit knowledge of cross-behavioural implications.

The benefits to the decision maker of the additional information of course come at a cost. The resource expense of (i) identifying or potentially generating estimates of links between health behaviours to inform health economic models and (ii) building adjoining economic models for behaviours linked to the targeted health behaviours will be significant. The case study presented in this thesis will provide perspective on the merit of this approach in practice.

1.4. Summary and Thesis Outline

Improving health-related behaviour in any population reduces the incidence of behaviour-related diseases and associated healthcare costs. Health economic models are used to inform and support decisions between competing strategies for

behaviour change in the UK, but the implications of links between health behaviours have not been considered. If such links are ignored, health economic model outputs could misinform decision makers and lead to sub-optimal resource allocation decisions. The framework described in this introduction can be used to guide development of health economic models of behaviour change strategies which account for cross-behavioural links.

A key aim of this thesis is to investigate bias in health economic evaluations of behaviour change strategies caused by omission of links between different behaviours. This thesis will test the proposed framework with a case study of the importance of the link between alcohol use and smoking for health economic models of smoking cessation interventions.

In doing so, this work contributes to the existing knowledge base in several ways. First, the thesis presents a narrative synthesis of current evidence on the link between alcohol and tobacco use. Second, the novel analysis of the dynamics of this link presented represents a clear and important contribution to this evidence base. Third, the individual-level simulation model to appraise competing strategies for smoking cessation presented represents an improvement on the prevailing mode of economic evaluation models in the field, in its capacity to incorporate complex patterns of long-term behaviour. Fourth, an economic appraisal of a pharmaceutical smoking cessation aid yet to be approved for use within the UK NHS using this model represents new evidence on the merit of a potentially important alternative for smoking cessation treatment. Fifth, the analysis explores the consequences of omission of the dynamics of smoking behaviour, including its link to alcohol use. Sixth, and crucially, the work allows better understanding of the merits and feasibility of using the proposed framework for economic evaluation in appraisals of strategies for further types of health-related behaviour.

The remainder of this thesis is structured as follows. Chapter 2 sets out the case study focusing on the link between alcohol and tobacco use and assesses the current knowledge base in the field. Chapters 3 and 4 present systematic reviews of economic appraisals of interventions to (i) aid smoking cessation and (ii) reduce

alcohol use. Chapter 5 contains an econometric analysis of the joint dynamics of smoking and alcohol use. Chapter 6 reports a health economic model of competing interventions for smoking cessation which ignores links to other health behaviours, based on an economic model used historically to support several intervention adoption decisions. Chapter 7 presents the methods and data for the Behavioural Interactions in Tobacco use (BIT) model, a *de novo* health economic model linking smoking and alcohol use changes to related diseases, health-related quality of life (HRQoL) and healthcare costs. Chapter 8 presents and analyses key results from this model. Chapter 9 contains discussion on key findings and the merit of the framework and concluding remarks.

2. Chapter 2: A Case Study of the Link between Alcohol Use and Smoking

In this thesis, the framework for economic appraisal of competing behaviour change strategies proposed in Chapter 1 is tested with a case study of the implications of the link between two specific health behaviours: alcohol use and smoking. NICE guidance for treatment and prevention of many different health behaviours is supported by evidence and there may be important links between health behaviours which are currently ignored by this evidence. Chapter 2 has two key objectives: (i) to highlight the reasons behind the choice of case study; and (ii) to present a broad picture of knowledge and research on links between alcohol and tobacco use, in order to identify where this work can contribute to the knowledge base.

The choice of case study was driven by four points. First, the financial burden of treating diseases linked to tobacco and alcohol use upon the NHS. Much public money is spent on policies to reduce alcohol and tobacco use, even more on treating alcohol and tobacco related disease. There is a great opportunity cost of these policies to other branches of the NHS and importance in making correct allocation decisions. Second, there is a link between alcohol and tobacco use, supported by theory and evidence. Third, the evidence of this link is as yet incomplete and further research could contribute to knowledge in this area. Evidence suggests a complex and dynamic link, but this is generally from data collected over a year or less and relatively little appears to be known about the link in the long-run. Fourth, data exist that can be used to better quantify the link between alcohol use and tobacco use. The following sections expand on these points, giving a sense of the current knowledge on the link between alcohol and tobacco use, and where evidence gaps lie.

2.1. The financial burden of tobacco and alcohol related disease to the NHS

Tobacco is the greatest single cause of illness and premature death in the UK and around half of tobacco smokers can expect to die from smoking-related diseases [18]. Approximately a fifth of UK adults smoke [19, 20]. The last Labour government announced new targets to reduce smoking prevalence in England to 10% of the adult population, through long-term policies concerning tobacco advertising, the protection of children from tobacco products, product regulation and labelling, tobacco tax, prevention of cigarette smuggling and NHS Stop Smoking services [19]. The current Conservative and Liberal Democrat coalition Government is committed to sustaining current funding on tobacco control in real terms and increasing duty on cigarettes above inflation, year on year [5].

Gross annual spending on tobacco policy is nearly £300 million, with the majority of resources funding NHS Stop Smoking services, anti-smuggling efforts and mass media campaigns [5]. The greatest cost of smoking to the UK purse is the burden of treating smoking-related disease. Estimates of the annual cost to the NHS range from £3.3 billion [21] to as high as £5.1 billion [22], and are rising as links to different diseases are discovered [21]. However, with smoking-related diseases putting a significant strain on healthcare resources, it is important to consider the financial benefits that the Government accrues from effective anti-smoking policies. The Government receives just under £10 billion in tobacco duties revenue every year [23], and this figure does not include additional revenue from effective anti-smuggling policy increasing the market share of legal trade.

Alcohol-related morbidity and mortality are significant concerns in the UK. Up to 70% of all peak-time admissions to accident and emergency departments are related to alcohol consumption [24] and the number of alcohol-related deaths more than doubled over the period 1991 to 2008 [25]. The estimated annual NHS cost of treating alcohol-related disease is also £3.3 billion [21]. Improving alcohol use is arguably as great a priority for public health practitioners as eradicating smoking. However, annual spending on alcohol information and educational campaigns is around £17 million [26], less than 6% of the annual sum estimated to be spent on

tobacco policy. In addition, Government revenues from alcohol duties are even greater than those from tobacco duties: over £10 billion [23].

The health implications of alcohol use are of course different to those linked to tobacco use, in that low alcohol consumption is not thought to be harmful. Nevertheless, in contrast to tobacco policy, few substantial steps were taken by Labour Governments between 1997 and 2005 to reduce alcohol consumption in the general population [24, 27]. Duty on alcohol increased only in line with inflation up to 2006 [28], while the 2003 Licensing Act notably removed fixed closing hours [29]. The same Act included provisions to increase police powers over disorderly drinking offences and clamp down on the sale of alcohol to minors, but the overriding narrative of alcohol policy in this period was one of enabling people to make informed choices rather than actively influencing behaviour [24, 27, 30]. After forming in May 2010, the coalition Government was quick to promise to tackle disorderly drinking and the sale of alcohol to children [31]. After investment in research on the potential health effect of minimum pricing for alcohol, the coalition Government recently scrapped plans to introduce a minimum price of at least 40p per unit of alcohol [32]. Prime Minister David Cameron justified this retraction on the basis that the resulting health effects were unproven [32], though the commissioned research concluded that a significant reduction in alcohol use and improvement in health would result from a move to minimum pricing [33].

The picture painted is that while modest sums are spent on tackling misuse of tobacco and alcohol, and large costs are imposed upon the NHS in treating illnesses attributable to drinking and smoking, even larger sums are accrued by the state every year in alcohol and tobacco duties. This may suggest a financial disincentive to reduce demand for alcohol and tobacco from the perspective of the state, but from an NHS viewpoint there is great incentive. The NHS budget is drawn from the revenue raised by UK taxes, but this does not mean the former increases proportionally with the latter. In the 2013 April Budget, spending on healthcare was unchanged from 2012 [34], while duties on alcohol and cigarettes increased [23]. Within the constraints of the NHS and Personal Social Services budget, reducing the cost of treating alcohol and tobacco disease allows reallocation of resources to other areas; strategies to improve alcohol and tobacco use in the population are

therefore highly valuable [21]. Aside from financial considerations, since 1948 and still relevant in the 2011 NHS constitution, the NHS has sought to improve health and well-being of patients as a core principle. NHS-funded strategies to improve alcohol and tobacco use are justified on the basis of resource allocation and principle, but do have an opportunity cost.

2.2. Theory and evidence of a link between alcohol and tobacco use

The opportunity cost of funding strategies to improve alcohol and tobacco use is significant, and the cost-effectiveness of such strategies could be mis-estimated if links to related lifestyle choices are ignored, but what evidence of a link between alcohol and tobacco use exists? This subsection presents evidence of links in consumption between the goods in the context of economic theory and further justifies state intervention to prevent misuse of alcohol and tobacco. The characteristics of alcohol and tobacco suggest that there is a relationship between use of each, and this is supported by evidence.

Microeconomic theory makes some assumptions about the way consumers' preferences behave. Specifically, three basic axioms about consumer preferences can be stated [35]:

1. Completeness. Any two goods or bundles of goods can be compared, so that an individual will either prefer one good or bundle to the other, or be indifferent between the two.
2. Reflexivity. Any good or bundle of goods is at least as good as itself.
3. Transitivity. If a consumer prefers good (or bundle of goods) X to good (or bundle of goods) Y and also prefers Y to good (or bundle of goods) Z, then the consumer by definition prefers X to Z.

In addition to these axioms, it is logical that preferences for some goods will be dependent on consumption of another good or goods. Specifically, *complements* are goods that are consumed together, in that in some sense the goods complement each other. An example of very strong complements is left and right shoes: people with two feet are likely only to buy a right shoe when they buy a left shoe to go with it [35]. Another example is that of toothpaste and toothbrushes. When goods such as these are consumed together in fixed proportions, they are

said to be perfect complements. In contrast, *substitutes* are goods that are consumed in place of each other. An individual might have a preference for classic cars, yet be indifferent towards car colour. In this simple hypothetical case, red classic cars and blue classic cars would be perfect substitutes.

Alcohol and nicotine have both been defined as addictive substances [36], and addiction can cause consumers to violate the basic axioms of preferences stated above. Addiction leads to consumers engaging in compulsive, repeated and unwanted use despite clearly harmful consequences, and often despite a strong desire to quit [37]. It follows that use of alcohol and tobacco products among addicts is frequently a mistake, and this could be judged to contravene the first axiom of consumer preferences. An individual may arguably incur negative utility from smoking a cigarette, by exacerbating a cough or incurring the wrath of their spouse, but smoke a cigarette despite this due to their addiction. In this way, it is plausible that addiction leads to actions contravening preferences.

Nehring has described the effect that this phenomenon might have on consumer behaviour by introducing the concept of second-order preferences [38]. While first-order preferences are those that are revealed by our behaviour in the marketplace, and those from which economists have derived the three basic axioms above, second-order preferences are preferences that we have about our own preferences [39]. Nehring describes an individual with a mild problem of excessive alcohol consumption, in that when faced with certain situations he will consume excessive amounts of alcohol (this is his first-order preference) [38]. However, this individual is aware of his problem and deep down wants to avoid drinking alcohol to excess (this is his second-order preference) [38]. Here, Nehring discusses the use of cognitive control by the individual to ensure his second-order preferences win out and the decremental effect this process of self-control has on utility [38]. But it is clear that the state could also intervene to ensure our second-order preferences are satisfied. Thus, when addicted cigarette smokers and alcohol drinkers have a deep-set desire to quit, government interventions to override first-order individual preferences can be justified.

If the state has a responsibility to help individuals limit their addictive behaviours, then understanding the interdependency of different addictive behaviours is necessary in order to provide an effective strategy, particularly in the context of limited financial resources. Attention now turns to the factors motivating similarities between alcohol and tobacco consumption, in order to better understand this interdependency.

Firstly there are 'external' factors which may influence the consumption of both tobacco and alcohol products. Such factors are termed 'external' because they are not specific to the individual, but characteristics of the environment in which consumers exist and make decisions. Tobacco and alcohol products are typically available for consumption from the same premises (supermarkets, convenience stores, public houses and bars) and in some cases (high level spirits and tobacco products in some supermarkets and convenience stores) grouped together in displays.

This in itself is perhaps unremarkable; many goods are sold concurrently in supermarkets and other premises. In addition though, the external effect of peer-group pressure on tobacco and alcohol consumption, particularly in terms of initiation of each at a young age, has been widely noted as important [40, 41]. Youths are more likely to smoke tobacco and drink alcohol when their friends exhibit similar behaviours [40, 41]. This finding is particular to youths in that purchasing, and in many contexts, consuming alcohol is illegal in the UK for those under eighteen years old, with similar laws in place in most other western countries. For adults, increased stress levels have been documented as leading to greater use of both alcohol and tobacco [42, 43], and to relapse in successful quitters of both [44, 45].

Secondly, there are 'internal' factors which might influence the consumption of both tobacco and alcohol. 'Internal' factors are defined as specific to the individual, and separate from context. Tobacco and alcohol are both products which are arguably consumed because of the acute pharmacological effects which each induces [46]. These pharmacological effects relate to changes in mood, behavioural performance and physiological responses [47].

Tobacco and alcohol products are also both addictive, through the respective chemical compounds nicotine and ethanol [48, 49]. This means that an individual's consumption of alcohol is positively influenced by their past consumption of alcohol, and the same relationship is true for an individual's consumption of tobacco.

Given these internal and external similarities, questions over the relationship between alcohol and tobacco behaviours arise. Specifically, whether alcohol and tobacco are complements, or substitutes, or whether there is no apparent relationship, is of interest.

The availability of both for sale together in supermarkets, convenience stores, bars and other premises cannot tell us much about whether the goods are substitutes or complements. Many substitutes are sold together, such as baguettes and bread loaves at a bakery; similarly, complements are often sold together, for example tyres and hub-caps at a mechanic's garage. Goods with no interdependencies are also regularly available from the same sales premises: fabric softener and celery are both available from most supermarkets, but it would be difficult to argue that there is a link in consumption of the two. Perhaps what is more suggestive here is that tobacco and alcohol products are in some cases two of only a very limited choice of products available to consume. This is the case in many public houses and bars. But while this reinforces the notion that tobacco and alcohol products might be linked in consumption, it cannot tell us whether the goods are complements or substitutes: snacks, contraceptives, alcohol products, tobacco products and soft drinks are all sold in most public houses, and some are complements of each other, some are substitutes for each other, and in some cases the relationship in consumption is not clear.

The implication of a peer effect on the relationship between consumption of alcohol and tobacco products is similarly unclear. Individuals who habitually smoke cigarettes and drink alcohol often initiate these habits in adolescence [50], when individuals within a peer group typically behave similarly. This has been widely argued to be a result of individuals conforming to rapidly established group norms [41, 51]. However, Urberg *et al* [41] have highlighted the importance of

friendship selection, which is often ignored: individuals will seek friendships with like-minded people.

Taking this into account, there are personality traits which can typify both alcohol drinkers and cigarette smokers: strong positive time preferences [52, 53] and arguably attraction to morally illicit activities. Both alcohol and tobacco offer immediate and short-term benefits in the form of positive sensations along with the prospect of future negative health consequences, attracting those who place much greater emphasis on the present than the future. Similarly, though consuming tobacco and alcohol is legal, if sometimes frowned upon, in the adult population, both are morally and legally illicit activities for adolescent children, the age group in which both behaviours are often initiated. This highlights that the distinction between 'external' and 'internal' factors discussed above can become blurred, but still leaves us unwise as to whether tobacco and alcohol are complements or substitutes. On the one hand, similar personality traits and peer group effects could lead individuals to adopt both drinking and smoking behaviours as complements; on the other hand, being a smoker could fulfil the peer group and individual personality needs of rebellion that alcohol would provide, and vice versa, meaning the two are substitutes.

Tobacco and alcohol are often consumed at the same sitting, or shortly after one another [47], and this certainly indicates that the products may be complements rather than substitutes. Perkins highlighted many ways in which nicotine and ethanol interact pharmacologically [47]. In terms of mood, nicotine attenuates the increase in intoxication due to alcohol and eliminates ethanol's sedative effects when blood alcohol concentration is falling [47], but nicotine can have an additive stimulant effect when blood alcohol concentration is rising. Individuals might use cigarettes to smooth the transition from sober to intoxicated and back to sober when drinking alcohol. In terms of performance, nicotine acts to attenuate the slowing of reaction times attributable to ethanol [47], which hints that tobacco is a complement to alcohol during activities requiring quick reactions in an ethanol-induced state. Results from physiological studies reinforce these findings [47]. The findings of Perkins indicate that tobacco and alcohol may often be consumed as complementary goods.

Johnson has since reviewed the neurochemical evidence for interactions between alcohol and nicotine [54]. Alcohol and nicotine appear to combine such that their ability on reinforcement mechanisms is additive. There is chemical evidence of a complementary relationship between drinking and smoking.

Stolerman and Jarvis [49] and Heidbreder *et al* [48] separately reviewed evidence that nicotine and ethanol, respectively, are both addictive substances. While Stolerman and Jarvis' review analysed patterns of use by smokers and the efficacy of nicotine replacement therapy (NRT) during attempts to withdraw from nicotine to assess the addictiveness of the drug and conclude strongly that the drug is addictive [49], the later review of the addictive properties of ethanol by Heidbreder *et al* [48] took a different approach. Here, the authors focused on the neurotransmitter dopamine, and specifically the effect that ethanol has on the dopamine D_3 receptors [48]. It was reported that evidence suggests intoxicating doses of ethanol can affect dopaminergic mechanisms and that the status of dopamine D_3 receptors may partially account for vulnerability to alcohol dependence [48]. But significantly, Heidbreder *et al* further reported that adaptive changes in the dopamine D_3 receptors can also result from repeated exposure to nicotine [48]. This hints that similar mechanisms in the brain are responsible for addiction to both nicotine and ethanol. However, a study by Larsson and Engel has reviewed neurochemical studies on ethanol and nicotine interactions and found no clear evidence that the two drugs act on the same sites in the brain [55]. Though there appears to be some evidence for a link between the addictiveness of ethanol and nicotine, it is not certain whether such a link exists and implications for the market relationship between tobacco and alcohol are unclear.

In summary, there is a theoretical argument for government intervention to influence both tobacco and alcohol behaviours, and there are several 'external' and 'internal' factors which suggest a relationship between alcohol consumption and tobacco consumption. The typical availability of alcohol and tobacco products from the same sales premises, the evidence for peer influence on the consumption of both, particularly in adolescence, the similar addictive mechanisms at work for both nicotine and ethanol, all suggest that the consumption decisions for alcohol and tobacco products are interdependent and it seems likely that the two types of

products are complements rather than substitutes. Evidence that tobacco and alcohol are often consumed together and on pharmacological interactions between nicotine and ethanol further suggests a complementary relationship. There remains much to be learnt about the relationship, though. A more detailed examination of research analysing the link between alcohol and tobacco use and in particular consideration of causality in this context helps establish what is currently known.

2.3. Further evidence: contemporaneous and inter-temporal links and causality

The previous section analysed evidence of a link between alcohol and tobacco use, with little reference to causation. Further studies on the relationship between alcohol and tobacco use were sought, with an interest in how use, or a change in use, of one substance, affects use of the other and whether studies can be used to infer causality between behaviours. An exploratory search in Google Scholar using combinations of the search terms 'drinking', 'alcohol', 'smoking', 'tobacco' and 'cigarettes' with terms such as 'secondary effect', 'knock-on' and 'related' was the starting point to identify studies. Further evidence was found by scanning reference lists, and performing citations searches in Web of Knowledge, for key studies. The aims, data, analysis method and findings of the forty eight studies identified are summarised in Table 32 of Appendix A.

The studies identified were varied in the types of data used. In many cases, trials have been used to investigate links between alcohol and tobacco use [56-75]. Elsewhere, survey data have been used to investigate correlation and where possible to attempt to establish causal links between alcohol use and tobacco use, and these data have been either *cross-sectional* [76-85] or *longitudinal* [86-95]. *Cross-sectional* data observe a set of individuals at the same point in time; *longitudinal* data track a sample of individuals over time, and are alternatively termed *panel* data [96].

Cross-sectional studies can be useful in identifying correlations between behaviours, but such links cannot to be said to be causal if they could be caused by another factor(s). For example, contemporaneous smoking and drinking could be explained by stress, and not necessarily imply a causal relationship between the

two behaviours. In order to understand causal relationships between tobacco and alcohol use, longitudinal data may be more useful. However, one event preceding another does not imply causality; careful analysis of longitudinal data is needed in order to infer causality.

The most widely used survey dataset in this area is the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), used in five different studies in Table 32 [79, 81, 89, 97, 98]. The first wave of NESARC, comprising data from over 43,000 individuals from the US general population, was conducted in 2001/2; a subsequent wave of data was collected in 2004/5 [99]. The vast majority of research in this area comes from the US; very little from the UK. The International Tobacco Control Four Country Survey (ITC-4), a cohort study of over 2,000 smokers in each of Australia, Canada, the UK and the US, is the only longitudinal dataset with UK person-specific data on both alcohol and tobacco use in Table 32 [63]. Another prospective study conducted in Finland collected information every four months for five to eight years, with a sample of ageing male smokers [86]. The remainder of survey data employed in Table 32 studies were either cross-sectional or recorded less frequently than annually. No identified study other than the Finnish study used more than three consecutive waves of annual longitudinal data. Therefore few identified studies analysed data with the potential to infer causal links between alcohol, and tobacco use over a number of years.

It appears from Table 32 that alcohol and tobacco use are positively correlated. Tobacco use and alcohol misuse co-occur in people, consistently across different populations [76, 78-82, 85, 98]. Further, tobacco use increases with alcohol consumption among those who smoke and drink [79]. Several studies have examined the immediate effect of alcohol upon smoking behaviour in individuals who drink and smoke using placebo-alcohol drinks to verify the effect [65, 69-71]. Alcohol increases smoking urge and enjoyment gained from smoking [65, 69-71]. There is strong evidence for, and explanation of, the positive correlation between alcohol use and smoking.

Interestingly, some UK general population data suggest that while smokers drink more than non-smokers, this may be predominantly due to lower drinking in

never-smokers: ex-smokers drank nearly as much as smokers [85]. This highlights two possible mechanisms at work: (i) the act of drinking induces smoking, as supported by studies of the immediate effect of alcohol upon smoking behaviour [65, 69-71] and the pharmacological properties of ethanol and nicotine [47]; (ii) other unobserved factor(s) influence both the propensity to drink and the propensity to smoke, driving correlation between the two. Several studies in Table 32 considered other observable factors which are predictors of tobacco and alcohol use, including age and gender [76, 79, 82, 91]. Factors which are difficult to observe might also be important, such as having an 'addictive' nature [100, 101].

Some research has addressed more specific questions about the relationship between tobacco and alcohol use, such as 'Does alcohol use predict smoking cessation?'. Here, there is evidence that those who drink to hazardous levels are less likely to quit smoking, and less likely to succeed in attempts to quit [56, 86, 88, 91, 93, 95, 102]. This tallies with evidence of alcohol inducing an urge to smoke [65, 70]. This effect may be true for hazardous drinkers, but not all drinkers, as drinking a moderate amount (less than 100g of alcohol per week) has been found to predict smoking cessation, relative to alcohol abstention [77]. Further, some studies found no significant correlation between alcohol use and smoking persistence [92, 103]. Two reviews considered evidence on the link between smoking cessation and *past* alcohol use problems [104, 105]; history of alcohol problems was judged as not important in predicting smoking cessation.

Research into tobacco use as a predictor of changes in alcohol use is divided into (i) studies of individuals meeting some published criteria for alcohol dependence and (ii) studies of non-dependent drinkers. The latter were fewer in number and generally found no effect upon alcohol use of changes in tobacco use [63, 90, 94], though one recent study found lifetime smoking cessation to predict lifetime alcohol cessation [97].

Studies of the role of tobacco in alcohol dependence treatment generally found a mild positive association between smoking and relapse to alcohol [57, 75, 89], but this was possibly offset by the beneficial effects of nicotine on alcohol withdrawal symptoms [74, 106]. Clinicians and researchers are interested in concurrent

treatment of smoking and alcohol problems in alcohol dependence patients [58]. Smoking cessation interventions for alcohol dependence patients have been shown to be beneficial for alcohol abstinence [107], possibly because smoking cessation drugs such as NRT, bupropion and varenicline attenuate alcohol withdrawal symptoms [108]. These drugs have been found to reduce alcohol consumption in non-dependent drinkers [67, 68]. Overall, concurrent interventions for smoking cessation and alcohol withdrawal are supported [58, 62, 64, 73].

This brief review has substantiated the tentative evidence from the previous section that tobacco use and alcohol use are positively correlated; they co-occur in individuals and complement each other in consumption. However, the range of research questions among studies reviewed here highlights the complexities of the link between alcohol use and tobacco use, while the datasets used perhaps highlight limited data in order to estimate causal long-term relationships between alcohol and tobacco use. Many studies used trial data to infer knock on effects from a change in tobacco (alcohol) use to changes in alcohol (tobacco) use, but trial follow-up is typically short, whereas the relationship between alcohol use and tobacco use may be long-term. Other studies have used survey data, but aside from one Finnish study the longitudinal datasets used have contained no more than three consecutive waves of annual data [86].

Hazardous drinkers are less likely to quit smoking; alcohol dependence patients who smoke are less likely to quit drinking; smoking cessation drugs may reduce alcohol use in dependent and non-dependent drinkers. All these factors may be important when considering the implications of the link between alcohol use and tobacco use for economic evaluations of behaviour change interventions.

There is a link between alcohol use and tobacco use; in ignorance of this, NICE guidance may be based on biased estimates of NB of competing strategies to improve alcohol and tobacco behaviours. This section suggests that the link is both complex and not fully understood. Little appears to be known about how alcohol and tobacco use causally interact in the long-term. Such information is pertinent to understanding long-term consequences of behaviour change strategies. With a view to adding to the existing literature and facilitating completion of this case

study through estimation of interactions between alcohol and tobacco use over time, the next section summarises the availability of surveys with data on both alcohol and tobacco use.

2.4. Available survey data on alcohol and tobacco use

The brief review above highlighted some datasets that could be used to analyse the interaction between alcohol and tobacco use, but these were limited in that alcohol and tobacco use data was collected infrequently, and over few time periods. The best data for understanding the inter-relation of alcohol and tobacco use over time will have regular data points over a long period with information on confounding factors that influence both alcohol and tobacco use, though the specific requirements will depend upon the information needed to inform cost-effectiveness models. This research is interested in the mis-estimation of cost-effectiveness in the UK context specifically, so UK data were prioritised. However, with consideration that more appropriate data may be available elsewhere, and considering that reasonable assumptions about transferability may be possible, non-UK datasets were also considered. A search for further survey datasets containing both alcohol and tobacco use data began with a search of the UK Data archive (http://www.data-archive.ac.uk) and continued with Google searches.

In the UK, the British Household Panel Survey (BHPS) collected individual-level data annually on a range of topics from an expanding panel of households from 1991 to 2009 [109], and has recently been replaced and incorporated by the *Understanding Society* longitudinal dataset project [110]. While the BHPS questionnaire did include questions on smoking behaviour, questions on alcohol consumption and frequency were absent from the survey. The survey included only one question relating to alcohol in each wave, enquiring if respondents have any health problems related to alcohol or drugs [109]. As a result, the BHPS is not adequate for the purpose of estimating the relationship between alcohol and tobacco behaviours.

Other British datasets are limited in their applicability to a study on long-term interactions between alcohol and tobacco use. Some datasets with information on

both alcohol and tobacco behaviour have been repeated cross-sectional surveys (Health Survey for England (HSE), Welsh Health Survey, Scottish Health Survey, Living Cost and Food Survey (LCS) (formerly the Expenditure and Food Survey), Smoking, Drinking and Drugs Use among Young People (SDD)). Again, cross-sectional data are only useful in identifying correlations between behaviour and so are of limited use for this thesis. The General Lifestyle Survey (GLS) (formerly the General Household Survey) switched from cross-sectional to quasi-longitudinal design in 2005, so that respondents now remain in the sample for four annual survey waves, but again this is of limited use. Others have been longitudinal in format, but collected data irregularly (1970 British Cohort Study, National Survey of Health and Development), or for specific sub-populations (English Longitudinal Study of Ageing (ELSA), Families and Children Study (FACS), Longitudinal study of Young People in England, Avon Longitudinal Study of Parents and Children (ALSPAC)).

The available British dataset with the most potential for use in this research is the Whitehall II study (also known as the Stress & Health Study). Whitehall II comprises a longitudinal cohort study that has followed an initial 10,308 men and women working as civil servants in London in 1985 aged 35 to 55. Detailed smoking and alcohol use data has been collected. However, there are several drawbacks for the purposes of this research. Firstly, the format of the questionnaire has been through many transformations (the study is currently in 'phase 10') in which details of smoking and drinking questions have been altered. In three phases, smoking and drinking questions have been absent. Secondly, data has been collected irregularly, and less frequently than annually: data collection has taken place once in each 'phase' of the study. Thirdly, Whitehall II contains a wealth of health data, but survey information on socio-economic variables that are known to co-vary with smoking and drinking behaviours is limited. Lastly, the Whitehall II sample is unrepresentative of the contemporary general population. The sample of middle-aged London-based civil servants in this study is significantly wealthier, better educated, more male and older than contemporary Britain.

With appropriate survey data lacking in England and Wales or the UK generally, data from overseas requires consideration. Similar publicly available national longitudinal surveys to the BHPS have been running in Australia, America and Germany, respectively. The Household, Income and Labour Dynamics in Australia (HILDA) survey has collected annual data on a range of topics from an initial sample of nearly 8,000 households since 2001 [111]. In each year, respondents have provided information about their smoking status and weekly smoking consumption, but weekly alcohol consumption cannot be derived from the first wave of data. In each year since 2002, data on (i) the frequency of drinking and (ii) the usual number of alcoholic drinks on a drinking day have also been collected.

The Panel Study of Income Dynamics (PSID) has been running in America since 1968 and is the longest running longitudinal household survey in the world [112]. The original focus was on the dynamics of poverty and so the PSID sample was disproportionately representative of low income households until 1999 whereby additional families had been recruited to make the sample representative of the general population [113]. In 1999, the PSID sample numbered nearly 7,000 households [113]. In 1997 the study switched from annual to biennial surveying, and in the same year respondents were first asked about their alcohol behaviour; questions on smoking status and cigarette consumption have been asked in every survey since conception. As a result, there are currently eight waves of available PSID data in which respondents have recorded alcohol and tobacco behaviours, spanning fourteen years. Questions on smoking have remained constant throughout the survey, demanding a 'Yes/No' response for smoking status and a qualitative response concerning daily cigarette consumption. Questions on alcohol behaviour changed in 2005. In the four surveys from 1997 to 2003 respondents were asked 'Do you ever drink alcoholic beverages?', and then asked to quantify their average daily consumption. In subsequent surveys the first alcohol question remains the same, but instead of average daily consumption, respondents have been asked to categorise their drinking frequency and report average alcoholic drink consumption on drinking days.

The German Socio-Economic Panel Study (SOEP) has collected data from an initial sample of nearly 11,000 households annually since 1984 [114]. SOEP respondents

have not been asked to describe their smoking behaviour in every questionnaire: smoking status and consumption questions were asked only in the 1999, 2001, 2002, 2004, 2006 and 2008 surveys. Questions on alcohol behaviour have been asked even less frequently: only in 2006 and 2008, waves 23 and 25 of the survey, have SOEP respondents described their alcoholic beverage consumption, for four categories of drink: spirits; beer; wine and champagne; mixed drinks. For each category of alcoholic beverage, respondents were asked to characterise their consumption using one of four options: '*never*'; '*seldom*'; '*once in a while*'; '*regularly*'.

The HILDA dataset is preferable to both PSID and SOEP in terms of regular longitudinal data on alcohol and tobacco use. Whereas HILDA contains repeated unchanging questions on both alcohol and tobacco behaviour every year at nine time points to the latest released results, PSID only tracks behaviour at two year intervals. An interval of twelve months between observations from an individual may be too lengthy to accurately record the impact of changes in behaviour, but it is certainly preferable compared with intervals of twenty four months. PSID also has fewer available waves of data with information on both alcohol and tobacco behaviour than HILDA. Though the SOEP sample size is larger than that of both HILDA and PSID, only two waves of data contain information on both alcohol and tobacco behaviours. In addition, translating the qualitative categories 'seldom', 'once in a while' and 'regularly' into alcohol consumption levels would require unproven assumptions.

HILDA data also compare favourably with those available from datasets in Table 32 for the purpose of estimating causal links between alcohol and tobacco use. Nevertheless, no identified studies have used HILDA to investigate links between tobacco and alcohol use. There is certainly scope to contribute to the existing knowledge base in this area using analysis of HILDA data.

2.5. Chapter Summary

A key aim of this chapter was to provide an overview of existing evidence of the link between alcohol and tobacco use. There are many factors suggestive of a relationship between alcohol and tobacco use. The two goods are often consumed together, affect the same sites of the brain in complementary ways, share addictive properties and are typically available for sale together. Survey and trial data have

been analysed by a multitude of researchers in an effort to understand different aspects of the relationship. Smoking and alcohol misuse co-occur in individuals; hazardous drinkers are less likely to quit smoking; alcohol dependence patients who smoke are less likely to quit drinking.

Despite the high number of publications in this area, relatively little is apparently known about long-term causal interactions between alcohol use and tobacco use. This could be a result of the scarcity of appropriate data, but HILDA contains recent, detailed, annual, longitudinal data on alcohol and tobacco use from a large sample of individuals. There is scope to undertake new analysis of these data and contribute to the existing evidence base in addition to taking steps towards answering the primary research question.

Another aim of this chapter was to explain the choice of case study. Smoking and excessive alcohol use place considerable burden upon NHS resources, and there is clear financial incentive from the perspective of the NHS to choose an optimal bundle of strategies to reduce this burden. There is also an argument for the state to intervene to help individuals to tackle their unhealthy behaviours, and satisfy their second order preferences, in the case of addictive goods.

It is believed that the case study is a justified choice because of the evidence base of a relationship between alcohol and tobacco use, as well as the burden of treating related diseases upon the NHS, in addition to the opportunity to add to existing evidence and better understand causal inter-temporal links between alcohol and tobacco use, for the purposes of economic appraisal of behaviour change strategies.

Chapter 5 will analyse the inter-related dynamics of alcohol use and smoking status using HILDA data, generating evidence that can be directly used in economic appraisal models. Before this though, Chapters 3 and 4 systematically identify and review existing economic appraisals of interventions to improve tobacco and alcohol behaviours, respectively. These two chapters help inform the modelling required to appraise strategies for smoking cessation while incorporating links to alcohol use and its consequences, and establish whether any such links have been considered in economic appraisals to date.

3. Chapter 3: Systematic review of economic evaluations of pharmaceutical interventions to aid smoking cessation

3.1. Introduction

In general, strategies to improve smoking behaviour can be first divided into (i) those targeted at individuals (e.g. counselling) and (ii) those targeted at populations (e.g. excise tax increases). Individual-level strategies can then be sub-divided into (i) those targeting smoking cessation and (ii) those targeting smoking reduction. The former are far more prevalent; as there is no healthy level of smoking, health bodies such as the NHS target smoking cessation in individuals. Smoking cessation strategies can be further sub-divided into (i) those designed to prompt quit attempts and (ii) those designed to assist quit attempts. This case study focuses on strategies to assist quit attempts.

The key aims of Chapter 3 are to (i) identify and (ii) evaluate published economic evaluations of interventions to assist smoking cessation aimed at individuals, in order to understand the methods and data employed. Of key interest was whether existing studies have considered a link to alcohol use. Evaluation of studies in the review included quality appraisal. The search strategy was tailored to identify studies with interventions that represent current standard practice in the UK.

It is well documented that quit attempts are substantially more successful when pharmacotherapy is employed [115] and experts have advised that pharmaceuticals should be used for smoking cessation unless there are specific contraindications for doing so [116]. The advice of an experienced General Practitioner (GP)[1] was sought and further reaffirmed that it is current standard practice in the UK to use pharmacology as an adjunctive therapy for patients willing to stop smoking. As a result, the tobacco search strategy included terms to identify relevant pharmacological interventions but the review did not include studies which evaluated the cost-effectiveness of interventions without pharmacological adjuncts.

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The drugs varenicline, bupropion and various NRT products are licensed for prescription use and recommended for use as an adjunct to smoking cessation along with motivational support [117, 118] (NRT products are available on general sale [118]).

3.2. Methods

An initial scoping exercise revealed a Health Technology Assessment (HTA) of bupropion and NRT for smoking cessation by Woolacott *et al*, including a comprehensive systematic review of existing economic evaluations, undertaken as part of the NHS Research and Development HTA Programme [118]. The systematic review identified 17 relevant full economic evaluations [119-135]. Searches were performed up to May 2001, so the review is now outdated and was performed before the drug varenicline was available. However, the search strategy used by the authors was considered to be of good quality and was pivotal in developing a contemporary search strategy.

The contemporary search comprised two stages. Firstly, the resources Econlit (via Ovid), NHS Economic Evaluation Database (NHS EED) (via york.ac.uk), Health Technology Assessment (via york.ac.uk) and the Health Management Information Consortium (HMIC) databases (via Ovid) were searched using search terms similar to those used by Woolacott *et al* [118]. These resources were selected to imitate as closely as possible the economic evaluation databases searched in 2001. As some databases searched by Woolacott *et al* were no longer in operation (EconBase) or not available at this author's institution (Office of Health Economics Economic Evaluation Database), the medical database MEDLINE was searched using a combination of search terms from Woolacott *et al* and the Centre for Reviews and Dissemination (CRD) search filter for economic evaluation studies (http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html) in order to capture any relevant studies that might otherwise have been missed. The search strategy is replicated in detail in Figure 22 of Appendix B.

The second stage of the contemporary search involved citation searches of the 17 studies included in Woolacott *et al*'s final review using the 'Times Cited' function

available within the Web of Knowledge database. It was reasoned that if the first stage of the search strategy was not comprehensive then any studies missed should be picked up by this second stage, as it is usual practice to cite preceding economic evaluation studies when reporting a cost-effectiveness analysis, even if a systematic search has not been used to identify informative data.

It was anticipated that the contemporary search strategy might identify additional comprehensive systematic review studies in the area, published after Woolacott *et al*. If such systematic reviews were found, it was reasoned that the sensitivity of the contemporary search strategy could be assessed by comparing the results of this systematic search with the results of other recent systematic reviews.

The search strategy was performed in February 2011. To identify additional studies published after this date, Ovid's Auto Alert service was utilised, whereby newly identified studies from the searches in Medline and EconLit were delivered monthly in citation and abstract form to this author's email address, up to the 1st of March 2014. These citations and abstracts were scanned to identify studies which improved on those identified by the original search in terms of methodology. However, those studies excluded at this stage and the reasons for exclusion were not recorded.

3.2.1. Inclusion and Exclusion Criteria

Selection criteria were specified in terms of study type, study population, types of intervention and other reasons. Identified studies were excluded if they failed to satisfy all inclusion criteria or met any of the exclusion criteria, specified below. Titles and abstract of all identified studies were screened for inclusion by one reviewer and full texts of potential inclusions were retrieved for further inspection.

Study Type. As described in Chapter 1, the NICE reference case states a preference for economic evaluations where effects are measured in QALYs [6]. Such cost-utility analyses (CUAs) are one type of economic evaluation. Different types of economic evaluations are defined by the nature of the consequences being assessed. Cost-effectiveness analyses (CEAs) quantify consequences in terms of a single, common effect that may differ in magnitude across comparators, such as life years [7]. CUAs are a sub-group of CEAs in which consequences are measured by utility. Cost-

benefit analyses (CBAs) measure both costs and consequences in monetary terms, allowing the absolute benefit of competing technologies to be assessed. It is worth noting that CEAs and CUAs can achieve this, if a monetary value is placed upon the measure of effect or utility. Cost-minimisation analyses (CMAs) assume equivalent consequences across comparators and base the analysis upon costs only and are rarely used in health technology evaluation studies [7]. This review included CUAs, CEAs, CBAs and CMAs. Partial economic evaluations, cost-of-illness studies, commentary type studies and unpublished work were excluded.

Study population. Smokers from the general population of any country worldwide were included. Sub-populations comprising military servicemen, pregnant women or patients with co-morbidities were excluded, as long-term health outcomes from these groups will differ, appropriate treatment may vary from that for the general smoking population, and it was difficult to incorporate this level of detail into the analysis of HILDA data detailed in Chapter 5.

Intervention Type. Studies assessing one or more alternative involving pharmacological treatment were included. Studies assessing alternatives involving counselling only and studies in which the alternatives were otherwise clearly not relevant to UK practice were excluded. Studies solely assessing interventions at the population level e.g. new legislature were excluded.

Other. Studies were excluded if an English language version was not available, or if a full text version could not be obtained.

3.2.2. Data Extraction and Analysis

The author extracted data from full economic evaluation studies included in the final review. Data extraction tables were developed using a published checklist for quality appraisal of economic evaluation studies [136]. The results of the systematic review were analysed in a narrative review but not synthesised. Systematic review studies included in the final review were discussed in the narrative review but did not have data formally extracted.

For the purpose of this review, and elsewhere in this thesis, economic evaluations alongside a trial are categorised as 'primary studies'. Economic evaluations that use modelling techniques to estimate costs and outcomes from multiple sources

are categorised as 'modelling studies'. Quality of modelling studies in the review was appraised using fifteen questions taken from peer reviewed quality appraisal recommendation documents [15, 136].

3.3. Results

Figure 2, Figure 3 and Figure 4 comprise the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram [137], describing information about the number of potentially relevant publications identified, included and excluded and aggregate reasons for exclusions. Reasons for exclusions at the final stage, after full publication retrievals, are reported separately in Table 35 of Appendix B.

Figure 2: Screening Abstracts Identified by the Search Strategy for Potential Inclusion

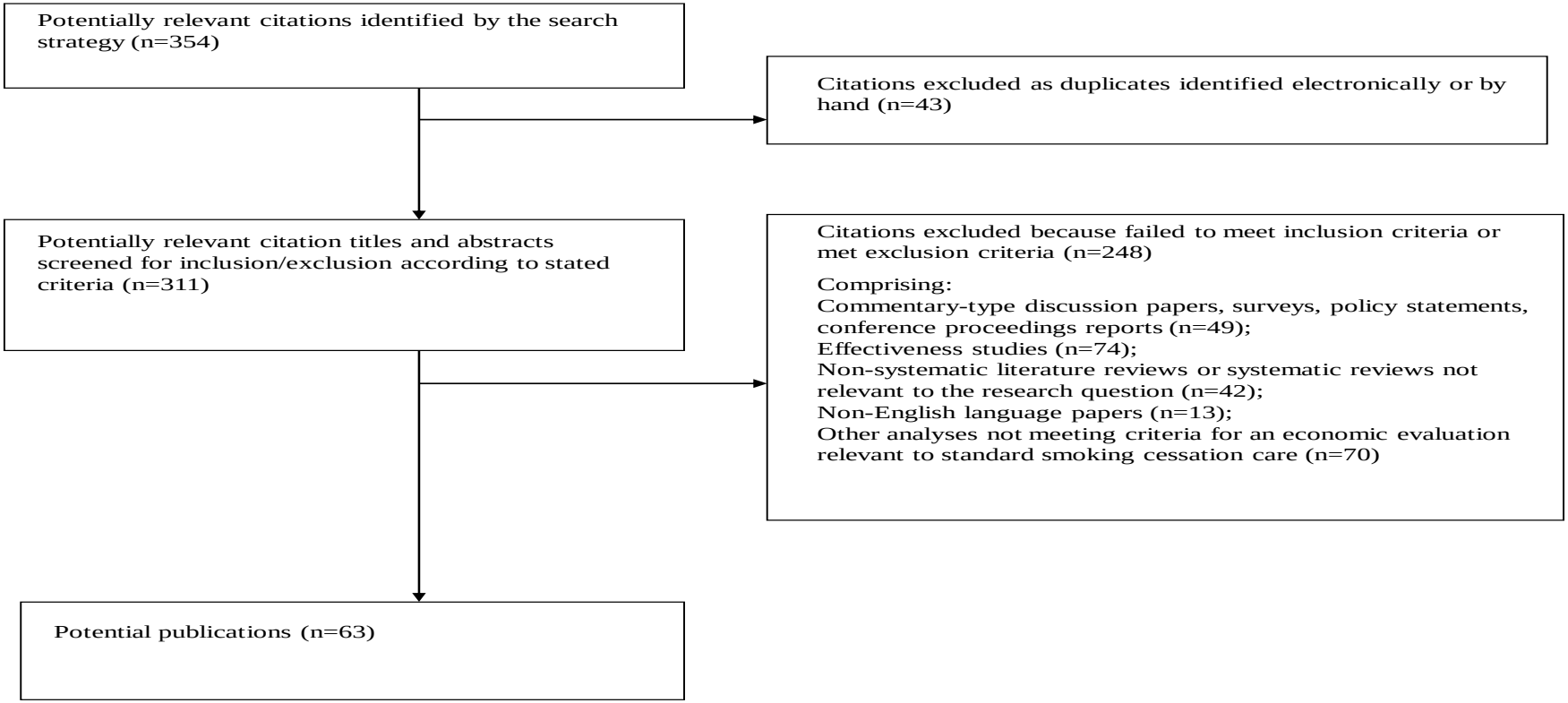


Figure 3: Screening Abstracts Identified by the Citation Search of Woolacott et al's Inclusions for Potential Inclusion

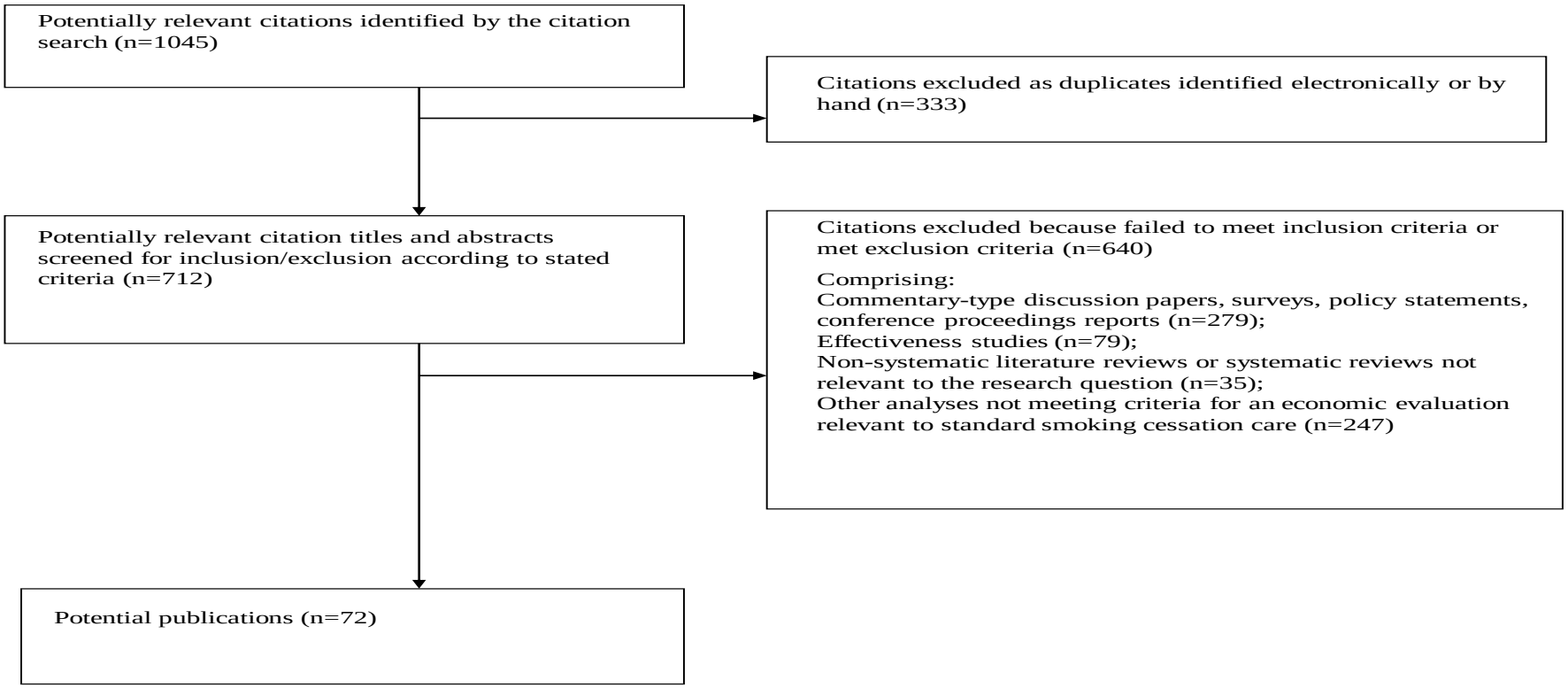
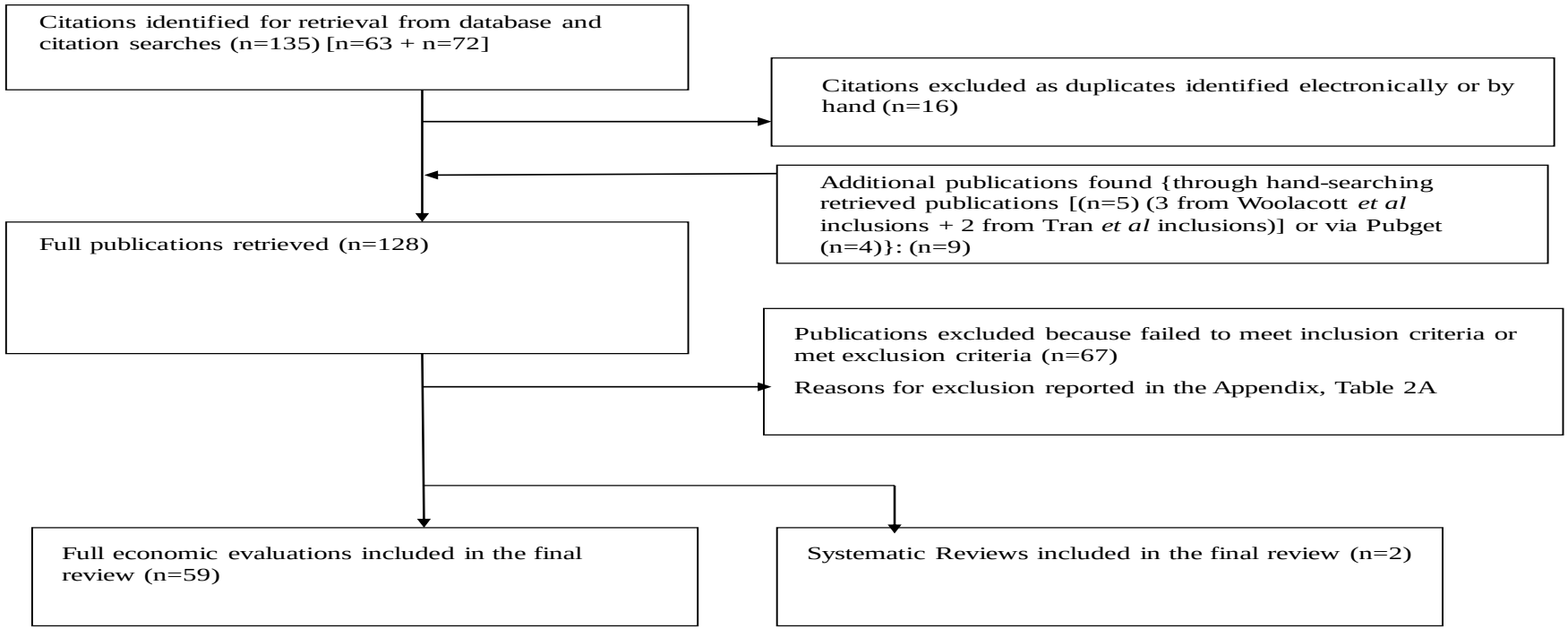


Figure 4: Screening Potential Inclusions for Final Inclusion



3.3.1. Study Characteristics

Fifty nine full economic evaluations were included in the final review, as shown in Figure 4. Table 33, which is displayed in Appendix B due to its size, presents key methods and results from each of these studies. None considered the effect of changing smoking behaviour upon alcohol behaviour, and the associated health and economic consequences.

For the purpose of this thesis an HTA is defined as a full economic evaluation of one or more health technology where the purpose of the assessment is to directly inform policy. By this definition five full HTA reports were identified by the search strategy. One of these studies was the report from Woolacott *et al* identified in the initial scoping exercise [118]; another was a more recent NICE-sponsored HTA report focusing on 'cut down to quit' interventions [138]; a third was a Canadian Agency for Drugs and Technologies in Health (CADTH) report on the cost-effectiveness of pharmacological interventions for smoking cessation [139]. Two further NICE-sponsored HTAs were identified: a Single Technology Appraisal (STA) of varenicline [117] (manufacturer's submission and Evidence Review Group report were classified as a single study) and a Rapid Review and report from a group at the University of York [140].

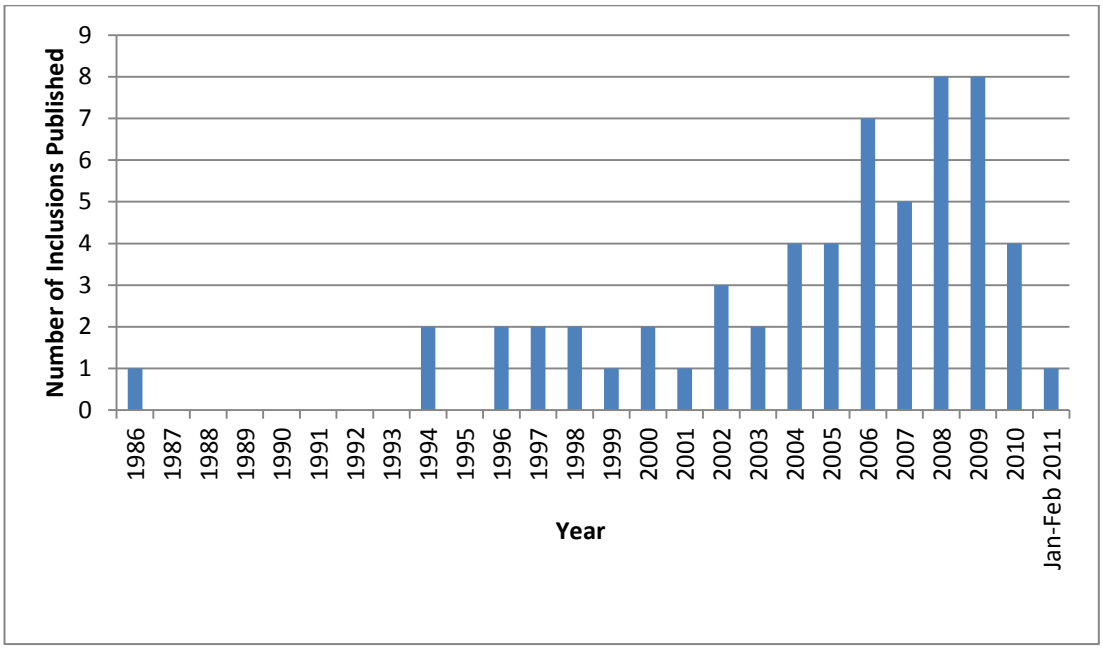
Table 1 and Figure 5 show the distribution of country settings and plot the pattern of publication dates for the fifty nine economic evaluations in the review. As Table 1 highlights, two fifths of included studies used an American study population and setting; nearly two thirds of all economic evaluations of interventions for smoking cessation are set in either America or the UK. The majority of the remainder of studies have used a European study population. However, the review does include studies set in Canada, Australia, Africa and East Asia. Figure 5 shows how the number of studies in this area published has increased markedly over time. The first full economic evaluation estimating the cost-effectiveness of a smoking cessation intervention involving pharmacology was published in 1986 [132]. No further studies satisfying the inclusion criteria were published until 1994, which saw the publication of two further relevant economic evaluations [119, 120]. From this point on there has been a general upward trend in the publication rate, with

sixteen relevant studies being published between January 2008 and December 2009.

Table 1: Country of Setting for Included Economic Evaluation Studies

Setting	Percentage of Total Inclusions	References
USA	39.0%	[124, 127, 128, 130, 132, 135, 141-157]
UK	23.7%	[117-120, 131, 133, 134, 138, 140, 158-162]
Holland	5.1%	[163-165]
Australia	5.1%	[166-168]
Sweden	5.1%	[169-171]
Switzerland	1.7%	[172]
Spain	1.7%	[173]
Canada	1.7%	[139]
Belgium	1.7%	[174]
Germany	1.7%	[175]
Finland	1.7%	[176]
Seychelles	1.7%	[177]
Japan	1.7%	[178]
South Korea	1.7%	[179]
Thailand	1.7%	[180]
Cross-border comparison	5.1%	[181-183]

Figure 5: Number of Included Economic Evaluations Published by Year



Eight of the fifty nine economic evaluation studies in the final review were primary studies [141, 142, 144, 146, 148, 154, 159, 175]; the remainder were modelling studies. Seven of the 8 primary studies in the review were CEAs [141, 142, 144, 146, 154, 159, 175] and all bar one of these used cost per additional quitter or average cost per quit as the main outcome measure; one study described costs and effects separately [144]. The remaining primary study was a CBA and reported net monetary benefit as the main outcome measure [148]. Eighteen of the 51 modelling studies in the review were CEAs: 5 of these 18 studies used a similar main outcome measure to the majority of primary studies in the review [143, 153, 157, 167, 168], but the remaining 13 studies measured outcomes in terms of cost per life year (LY) gained [119, 120, 131-135, 145, 160, 172, 177, 180, 182]. Two of these 18 studies undertook both a CEA and a CBA [143, 157]. Twenty seven of the 51 modelling studies in the review were CUAs [117, 118, 124, 127, 134, 138-140, 147, 151, 156, 158, 161-166, 169-171, 174, 176, 178, 179, 181, 183] and all bar one of these 27 studies used cost per QALY gained as their main outcome measure: the exception reported cost per Disability-Adjusted Life Year (DALY) gained [166]. The remaining 5 modelling studies in the review were CBAs: 2 of these 5 studies used a benefit-to-cost ratio as the main outcome measure [128, 152], while 3 reported outcomes as net monetary benefit from the perspective of an employer [130, 149, 155].

It was possible to sub-divide the 51 modelling studies by model structure type. All bar one of the 51 modelling studies used cohort state-transition models; the remaining study used an individual-level simulation model [145]. Cohort models follow a group of identical individuals through a process, typically comprising health states in health technology appraisal applications. Thus, cohort models can be used to characterise the 'average' experience of an individual [10]. If differences between individuals are important, cohort models can account for attributes such as age or gender by subdividing health states [14], but the number of dimensions will rise exponentially with subdivisions, and modelling multiple differences within cohorts can soon become complex. Individual-level models simulate the movement of each individual with different attributes through a process [14], meaning the attribution of individual characteristics is less cumbersome. There are calls for individual-level analyses to supersede cohort analyses as the preferred technique for health economic evaluations [184].

The study which used an individual-level simulation approach evaluated the use of a genetic test to tailor smoking cessation treatment [145]. This approach was perhaps selected over a cohort model for ease of incorporating the complexity of genetic differences between individuals, a complexity which other models did not have. However, a cohort state-transition modelling approach is limiting even when genetic complexities are not considered, for example in flexible projection of smoking status beyond trial end points.

Many of the recent modelling studies identified [117, 151, 164, 170, 171, 174, 176, 179, 181, 183] used the Benefits of Smoking Cessation on Outcomes (BENESCO) model, developed for use by Howard *et al* in 2008 [147]. This model is an extension of the Health and Economic Consequences of Smoking (HECOS) model, developed and implemented by Orme *et al* in 2001 [131] and later used by Godfrey *et al* [160] . The BENESCO model is a state transition cohort model with a lifetime perspective, which has gained international use, but is subject to key limitations. The model does not allow for the possibility that a patient may have two smoking-related diseases at the same time and does not allow for the possibility of more than a single quit attempt. These limitations are perhaps explained by the practical constraints of modelling within a cohort framework.

Other cohort modelling studies in the review have incorporated a constant underlying quit rate, but have not incorporated a relapse rate which decreases with time since quit [118, 140, 160], a real life complexity that the BENESCO model does boast. Relapse rates assumed post trial follow up varied in general across modelling studies in Table 33, and were typically based on dated information from external samples with limited follow up. Perhaps the best example of relapse data was from an eight year follow-up study of 1686 patients in an RCT of NRT treatment (840 were successfully contacted in 1999) [185], used to inform one study in the review [160]. None of the studies included the costs or consequences of adverse events from smoking cessation interventions in analyses.

As shown in Table 33, interventions under comparison varied across the 59 economic evaluation studies. The vast majority of included studies evaluated one or more alternatives involving some form of NRT [117-120, 124, 127, 128, 130-135, 138-141, 143-169, 172-175, 177, 179-183]. Bupropion was licensed for smoking cessation in the UK in 2000 [186] and the majority of studies in the review published since the turn of the century include bupropion in one or more study alternative [117, 118, 128, 130, 131, 139, 140, 142-145, 147-153, 158-170, 172, 174, 175, 177, 179, 182, 183]. Varenicline was licensed as an aid to smoking cessation in 2006 [187] and similarly the overwhelming majority of included studies published since 2006 include varenicline in one or more study alternatives [117, 139, 143, 145, 147, 151, 158, 159, 164, 170, 171, 174, 176, 178, 179, 181, 183]. The majority of studies aimed to compare the optimality of different pharmaceutical interventions [117-120, 124, 127, 130, 132, 134, 135, 139-143, 145-148, 151, 153, 155, 156, 161-172, 174-179, 181-183]. In these studies it was typical to offer some form of support from a health professional in conjunction with pharmaceuticals, and some studies also tested the relative optimality of different levels of support. For a significant minority of studies though, the aim was to assess the optimality of some service configuration including pharmaceuticals, where the optimality of the pharmaceuticals themselves was arguably of secondary importance [128, 131, 133, 138, 152, 154, 157-159, 180]. Three studies specifically analysed different counselling intensities in alternatives involving pharmacological treatment [144, 149, 150].

Forty three of the 59 studies in the review used 12 month cessation rates as the primary measure of intervention effectiveness. Eighteen of these 43 studies

reported that continuous cessation was measured [117, 118, 138, 139, 148, 151, 158, 161, 163, 169-171, 176-178, 180, 181, 183]; 6 of these 43 studies used point prevalence estimates [130, 146, 149, 150, 165, 182]. The remaining 19 of these 43 studies did not elaborate on their definition of 12 month smoking cessation [119, 127, 128, 132, 134, 135, 140, 142, 143, 147, 153, 162, 164, 166, 167, 172-175]. Twelve studies reported using biochemically confirmed smoking cessation estimates [127, 130, 134, 139, 142, 147, 148, 158, 165, 175, 176, 178]. Aside from these forty three studies, eleven studies in the review used cessation rates at less than 12 months from intervention as the primary effectiveness measure [124, 133, 141, 144, 145, 154-156, 159, 160, 168]. 3 of these eleven studies reported measuring continuous cessation [145, 156, 168] while 2 of these eleven studies used self-reported point prevalence estimates [144, 154]. Two of these eleven studies used biochemically confirmed effectiveness data [159, 160]; the time from intervention to measurement of effectiveness ranged from 4 weeks [159, 160] to 8 months [144] across the 11 studies. The remaining 5 studies in the review did not clearly define the period over which cessation was measured.

Nineteen of the fifty nine studies in the review stated that their study population was motivated to quit smoking [117, 134, 139, 141, 142, 146, 149-151, 154, 158-160, 162, 166, 170, 171, 176, 179]. Seventeen further studies accounted for willingness to quit by assuming a stated percentage of the study population were motivated to stop smoking [118, 124, 128, 133, 140, 145, 147, 153, 156, 159, 164, 169, 172, 174, 177, 182, 183]. Twenty one studies did not make any explicit assumptions about motivation to quit [119, 120, 127, 130-132, 135, 143, 144, 148, 152, 155, 157, 159, 161, 163, 167, 168, 173, 175, 178, 180]. Of the 2 remaining studies in the review, one explicitly stated that the study population did not need to be motivated to stop smoking [165], while one explicitly excluded smokers willing and able to make an abrupt quit attempt in order to answer their research question [138].

The main difference in the costing approach taken in the 59 economic evaluation studies in the review was between studies that included future medical costs for smoking-related diseases alongside intervention costs. The 8 primary studies all had a time horizon of 1 year or less and so did not include future smoking-related disease medical costs (SRDMC). Five of fifty one modelling studies had similarly short time horizons and so did not include SRDMC [130, 153, 155, 167, 168]. Of the remaining 46 modelling studies, 21 included SRDMC [117, 120, 128, 131, 139, 140, 147, 151, 160,

[164, 166, 169-171, 173, 174, 176, 179-181, 183] and 3 studies (performed from the perspective of an employer or insurer) included all future medical expenses [143, 152, 157]. There was variation in which diseases qualified as smoking-related diseases between studies, but these were defined as chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), lung cancer, stroke and asthma exacerbations in the BENESCO model. One modelling study included SRMDC for CHD only[173] .

3.3.2. Study Findings

Table 33 shows that when an alternative including varenicline was compared to an alternative including bupropion and/or an alternative including NRT in any of the included economic evaluation studies, the alternative including varenicline was consistently the most effective. In every study where an alternative including bupropion was compared to one or more alternatives involving NRT, the alternative involving bupropion was more effective. Similarly, alternatives involving NRT were consistently more effective than alternatives where pharmaceutical treatment was absent. In addition, increased support alongside drug treatment led to higher effectiveness when this was tested and alternatives were generally more effective when the treatment period was extended.

Where costs were fully reported, intervention costs for alternatives involving NRT, bupropion and varenicline were similar, with intervention costs for alternatives involving NRT often the most expensive because of the higher drug cost. When SRDMC were included, the most effective alternatives generally became the least costly, as long-term cost savings are incurred from the prevention of smoking-related diseases. In the three studies where future general medical expenses were estimated, cost savings from the prevention of smoking related diseases were generally cancelled out by medical costs incurred in an extended life span [143, 152, 157].

In Table 33, where a full incremental analysis was performed by the authors the optimal alternative is displayed in bold font. It can be seen that in all but one study [168], the most effective alternative was also the optimal alternative, and even this anomaly might be explained by the short time horizon used by Shearer and Shanahan [168]. Interventions involving varenicline were therefore consistently the optimal alternative in recent studies.

3.3.3. Study Quality

The results of the quality appraisal of modelling studies are presented in Table 34 of Appendix B. Overall, the quality of reporting, data identification and analysis was varied but reasonable across the 51 modelling studies. All studies posed a well-defined and answerable research question and reported valid conclusions given the data presented.

The three included HTA reports, the STA of varenicline and the NICE Rapid Review, along with a handful of other studies, used a systematic search and review of the literature to inform model parameter evidence [117-119, 132, 133, 138-140, 161, 166, 168], though two of these used findings from previously published systematic reviews [133, 166]. The remainder reported sources of model parameter data but it was not clear in these studies if the best available data was used.

Philips *et al* identified types of uncertainty in health economic models: parameter, structural, methodological and population heterogeneity [15]. All bar 3 of 51 studies assessed [120, 128, 167] made some attempt to analyse uncertainty in their model results and 19 studies [117, 127, 139, 147, 151, 156, 162, 164-166, 169-171, 174, 176, 178-181] used probabilistic methods to analyse parameter uncertainty. Only 4 studies [117, 169-171] made some attempt to analyse all four types of uncertainty.

Generally, more recent studies, such as those using the BENESCO model, were of higher quality, but this trend was not pronounced. Notably, the quality appraisal checklist does not highlight the structural limitations of the BENESCO model and other cohort models, noted above. HTA studies generally satisfied more of the fifteen quality criteria than peer-reviewed journal studies. Only one study satisfied all elements of the quality appraisal [117].

3.3.4. Search Sensitivity

It was anticipated that the search strategy would identify any relevant and recently published comprehensive systematic review studies. As reported above, one of the economic evaluation studies identified was a CADTH health technology assessment by Tran *et al* published in 2010 [139]. A key aim of the study was to compare the cost-effectiveness of pharmacological agents, with or without behavioural support programs, for smoking cessation and an extensive search of 10 databases

(MEDLINE, Embase, BIOSIS Previews, PsycINFO, the Cochrane library, CINAHL, HEED, DARE, NHS EED, HTA) was undertaken in February 2009 with search updates running to March 2010 [139].

Tran *et al* included 25 full economic evaluation studies in their final review [118, 119, 130, 133, 140, 142, 143, 145, 147, 148, 155, 163-170, 173, 177, 178, 182, 188, 189]; all of these were identified by the search performed here, though one was excluded from the final review because the full text for the study was unobtainable [189]. This suggests that the search performed here was comprehensive, but Tran *et al* also reported a list of 101 excluded studies [139], which enables further analysis of the relative sensitivity of the current search strategy. Several studies were included in the final review of the current study that were not identified by Tran *et al* [117, 151, 154, 158, 159, 164, 165, 171, 174, 176, 179, 181, 183], but all of these bar two [154, 165] were published after the date of Tran *et al*'s initial search. It is possible that one of these studies was excluded by Tran *et al* at an early stage as the authors estimated the cost-effectiveness of reimbursing smokers for pharmacological treatment rather than the treatment itself [165], but it is difficult to explain why Tran et al failed to identify the other [154]. Several studies were identified and excluded by Tran *et al* but included by this study [120, 124, 127, 131, 132, 134, 135, 138, 149, 150, 156, 161, 172, 175, 180]. Further, there were 23 studies that were identified and excluded by Tran *et al* that were not identified by this search strategy [190-212]; none, however, met the inclusion criteria for the current review. Overall the results from Tran *et al* suggest that the search strategy used here was highly sensitive. This suggests that scanning references and performing citation searches in Web of Knowledge using a selection of studies in the area of interest was in this instance a comprehensive and significantly less time consuming search method than employing highly sensitive and comprehensive search strategies within a selection of databases.

In addition to the economic evaluation studies which used systematic reviews to inform model parameters, the search also yielded 2 stand alone systematic review studies in the area [115, 213].

Zimovetz *et al* aimed to identify and review economic evaluations of varenicline for smoking cessation by searching three key databases (MEDLINE, the Cochrane

Library and NHS EED) and additional sources for unpublished studies up to October 2009 [213]. Ten relevant published economic evaluation studies were identified [143, 145, 147, 148, 164, 170, 174, 176, 178, 181], all of which were identified by this author's search strategy. Ten further unpublished studies including conference abstracts and presentations were identified, of which one was identified as a full published economic evaluation by our search [179].

Faulkner [115] also reviewed economic evaluations of varenicline for smoking cessation in a 2009 publication, but did not report a search strategy to identify studies. Six relevant studies were included in Faulkner's review [143, 145, 147, 148, 164, 170], comprising the studies included by Zimovetz *et al* that were published in 2008 or earlier.

3.3.5. Recently Identified Studies

Since this systematic search was conducted, there have been signs that the mode of modelling approach in the area is moving from the cohort analyses that have been prevalent in the review, to individual-level analyses. The Smoking Cessation Treatment and Outcomes Patterns (STOP) Simulation is a recently published lifetime individual-level simulation model for appraisal of smoking cessation strategies [214, 215]. Through a patient-level approach, the STOP model is able to overcome the key structural constraints of cohort models identified and incorporate multiple changes in smoking status over the life course.

Briefly, the model works by simulating individuals from trial data characteristics and predicting smoking cessation success through 'driving' equations for abstinence at 12 weeks and relapse up to 52 weeks, estimated using trial outcome data and sample characteristics. Times to relapse and next quit attempt are then based on an analysis of a cross-sectional web-based survey of 1078 current and former smokers in the US [216] and a four year study of smoking behaviour among 548 US college students [217], respectively [214]. If relapsers are predicted to attempt to quit again after 52 weeks, their one year quit attempt outcome is again predicted from the driving equations, with characteristics such as age updated and controlled for.

The STOP model considers similar smoking-related diseases to the BENESCO model, and has been used to compare a situation where only one quit attempt at the start of the model is allowed with a situation where multiple quit attempts over the life course are allowed [214]. Unsurprisingly, the latter predicts fewer smoking related disease incidences and more life years [214]. Comparison of competing strategies to aid smoking cessation using the model is as yet untested.

Strengths of the STOP model are the ability to predict cessation attempt outcomes using patient characteristics and the ability to model multiple quit attempts over the life course, but the data to predict times to quit attempt and relapse after trial data end points are again a key limitation. From the brief review in Chapter 2 and the studies identified here it is apparent that long-run patterns of smoking behaviour are not well evidenced or understood.

3.4. Discussion

This chapter has reported the results of a systematic review of economic evaluations of smoking cessation interventions targeting individuals. Crucially, while many economic evaluations have been performed in this area, with increasing volumes of publications in recent years, no study has considered the impact of changing an individual's smoking behaviour upon their alcohol behaviour, and subsequent cost and health consequences.

Modelling techniques have been widely and increasingly used to incorporate long-run health and health-related cost outcomes of smoking cessation strategies, in line with NICE guidance [6]. The model types employed in identified studies is of great interest. Cohort state-transition models have been widely used in the appraisal of health technologies [184], and this approach could be described as 'standard practice' for economic appraisal of strategies to aid smoking cessation, having been employed in all bar one [145] of the 51 modelling studies originally identified. The cohort modelling approach has imposed limitations on these studies though. Due to the difficulty of modelling multiple lifetime changes in smoking status within a cohort, these studies have made simple and unrealistic assumptions about behavioural patterns over the life course. The most widely used model structure, the BENESCO model, assumes no future smoking quits are possible after an initial quit attempt. Patient-level modelling offers the flexibility

to accurately capture complex behavioural patterns over time, and should be the future platform for economic analyses in this area.

The recently published STOP simulation model [214, 215] demonstrates the benefits of individual-level simulation to address appraisal decisions in this area. The model improves on others in the field in allowing multiple quit attempts and relapses over the life course and estimating cessation attempt outcomes using trial patient characteristics. However, the data to predict smoking behaviour patterns after trial follow-up endpoints are limited. Lack of knowledge about individual behavioural patterns over time has been a theme of the studies analysed in this chapter and the brief review of evidence in Chapter 2. Analysis of the longitudinal individual-level data available in the HILDA dataset detailed in Chapter 5 will be a valuable contribution to the knowledge base in this area. The long-term patterns of smoking behaviour are clearly an important factor of the value of strategies to aid smoking cessation attempts.

The results from the many economic evaluations in the review strongly suggest that individual-level smoking cessation aids are a cost-effective use of healthcare resources. Since the pharmaceutical varenicline was licensed for use as an aid to smoking cessation in 2006, an alternative involving a course of varenicline has been evaluated in the vast majority of studies meeting the inclusion criteria, and the overwhelming message from the results of these studies is that interventions involving varenicline are the most effective and most cost-effective strategies for smoking cessation. To what extent this result is due to the flawed modelling assumptions of cohort studies identified is not clear from this review, but will become clearer when results from a 'standard practice' cohort model in Chapter 6 are compared with those from a patient-level model in Chapter 8.

An individual's smoking status has a direct impact upon their health in the long-term and associated long-term healthcare costs. A lesson from this chapter is that the way these costs are accounted for in analyses can have an impact upon results. When long-term smoking-related disease costs were included in studies, the most effective study alternatives were highly cost-effective, and in some cases cost-saving, in comparison to other alternatives. The NICE reference case dictates that

such costs should be included, but future medical costs unrelated to the condition or technology of interest should not [6].

Which diseases qualify as smoking-related is a further area of contention. The BENESCO model has emerged as the most widely implemented model structure for economic evaluations of interventions for smoking cessation in individuals, and includes COPD, CHD, lung cancer, strokes and asthma exacerbations as smoking-related diseases. Methods and data to link smoking status to health in the STA of varenicline in the review will be useful to inform both the 'standard practice' model analysis in Chapter 6 and the individual-level analysis in Chapter 8.

3.5. Chapter Summary

The review presented in this chapter has highlighted that while many economic evaluations of pharmaceutical aids to smoking cessation have been performed, none have considered the link to alcohol use and its health-related consequences. Modelling techniques have been widely used to extrapolate beyond trial endpoints and incorporate long-run consequences of smoking cessation. The vast majority of modelling studies have used cohort model structures, and this has contributed to various unrealistic assumptions about long-run behaviour which may have influenced results. Regardless, cohort modelling studies and the BENESCO model in particular have become standard practice in the field. Individual-level models offer the flexibility to incorporate complex behavioural patterns over the life course, as demonstrated by the recent STOP model [214], and may well become the standard framework for economic evaluation of strategies for smoking cessation in the future. Analysis in Chapter 8 allows further evaluation of the relative benefits of individual-level modelling in this area.

This review has also served to further highlight the lack of evidence on long-term patterns of smoking behaviour. This could be of great consequence for economic evaluation estimates: long-term patterns of smoking behaviour, and what determines these patterns are clearly important for cost-effectiveness estimates. This chapter has thus further motivated the analysis of HILDA data in Chapter 5. Before this though, Chapter 4 presents a systematic review of economic evaluations of strategies to improve alcohol use.

4. Chapter 4: Systematic Review of economic evaluations of individual-level interventions to change alcohol behaviour

4.1. Introduction

While the review of economic evaluations of treatments for smoking cessation in the previous chapter focussed on interventions involving pharmacotherapy, standard alcohol treatment does not routinely include pharmacological treatment and so no such restrictions were in place here. Further, while individual-level treatment to change smoking behaviour aims for cessation, the goal in alcohol treatment is sometimes reducing consumption and/or changing consumption patterns, rather than abstinence. As a result, the scope of interventions amenable to current standard practice for alcohol treatment for individuals in the UK was considered to be broad.

The key aims of Chapter 4 are to (i) identify and (ii) evaluate published economic evaluations of alcohol reduction and cessation interventions aimed at individuals, in order to understand the methods and data employed, with the need to link alcohol use to health consequences in Chapter 7 in mind, but with keen interest also in whether links to smoking behaviour have been considered. Evaluation of studies in the review included quality appraisal. The search strategy was tailored to identify studies with interventions that represent current standard practice in the UK.

4.2. Methods

An initial scoping exercise identified a systematic review of economic evaluations of alcohol treatment, published in 2010 by Barbosa *et al* [218]. Further investigation revealed that this systematic review and a subsequent economic evaluation study formed part of a successful UK PhD thesis by the lead author [219]. The inclusion and exclusion criteria for the review were similar to those needed for the current review and the search timeline ran to February 2009 [218]. The search was applied primarily to the database NHS EED, but the authors correctly observed that this database searches MEDLINE, EMBASE, PsychINFO and CINAHL

for potential economic evaluations [218]. In addition, Barbosa *et al* performed a separate search in MEDLINE covering the period January 2008 to February 2009 for relevant records not yet reviewed and added to the NHS EED [218]. The search terms were appropriate and thorough; therefore an update to Barbosa *et al*'s search in NHS EED (via york.ac.uk, 1st January 2009 to 28th February 2011) and MEDLINE (via Ovid, 1st January 2009 to 28th February 2011) was deemed almost sufficient for the present review. In addition, a similar search of the database Health Technology Assessment (via york.ac.uk) was run for all years up to 28th February 2011 as the previous strategy may have been insensitive to important health technology assessments only otherwise available directly from individual funding agencies around the world [220]. Reference lists from each included study were screened for potential inclusions and the search strategy is replicated in full in Figure 23 of Appendix C.

Though Barbosa *et al* did not cite any previous systematic review studies in the area, it was anticipated that the contemporary search strategy might identify additional relevant systematic review studies [218]. It was hypothesised that the results from any such study, plus screening the references of included studies, would provide evidence for the degree of sensitivity of the search strategy.

As stated, all searches were run in February 2011. As for the review reported in the previous chapter, Ovid's Auto Alert service was utilised to identify additional studies published after this date, whereby newly identified studies from the searches in Medline and EconLit were delivered monthly in citation and abstract form to this author's email address, up to the 1st of March 2014. These citations and abstracts were scanned to identify studies which improved on those identified by the original search in terms of methodology. However, those studies excluded at this stage and the reasons for exclusion were not recorded.

4.2.1. Inclusion and Exclusion Criteria

Selection criteria were specified in terms of study type, study population, types of intervention and other reasons. Identified studies were excluded if they failed to satisfy all inclusion criteria or met any of the exclusion criteria, specified below. Titles and abstract of all identified studies were screened for inclusion by one reviewer and full texts of potential inclusions were retrieved for further inspection.

Study Type. Full economic evaluations (CEAs, CUAs, CBAs or CMAs) and systematic reviews of full economic evaluations were included. Partial economic evaluations, cost-of-illness studies, methodological studies, commentary type studies and unpublished work were excluded.

Study population. Individuals from any country worldwide at which treatment to alter alcohol consumption was directed were included. Sub-populations comprising military servicemen, pregnant women or patients with co-morbidities were excluded, as long-term health outcomes from these groups will differ, appropriate treatment may vary from that for the general population, and it was difficult to incorporate this level of detail into the analysis of HILDA data in Chapter 5.

Intervention Type. Studies assessing one or more strategy to counter excessive alcohol use, alcohol abuse, problem drinking or alcohol dependence were included. Studies solely assessing screening alternatives without follow-up treatment were excluded. Studies solely assessing interventions at the population level e.g. new legislature were excluded.

Other. Studies were excluded if an English language version was not available, or if a full text version could not be obtained.

4.2.2. Data Extraction and Analysis

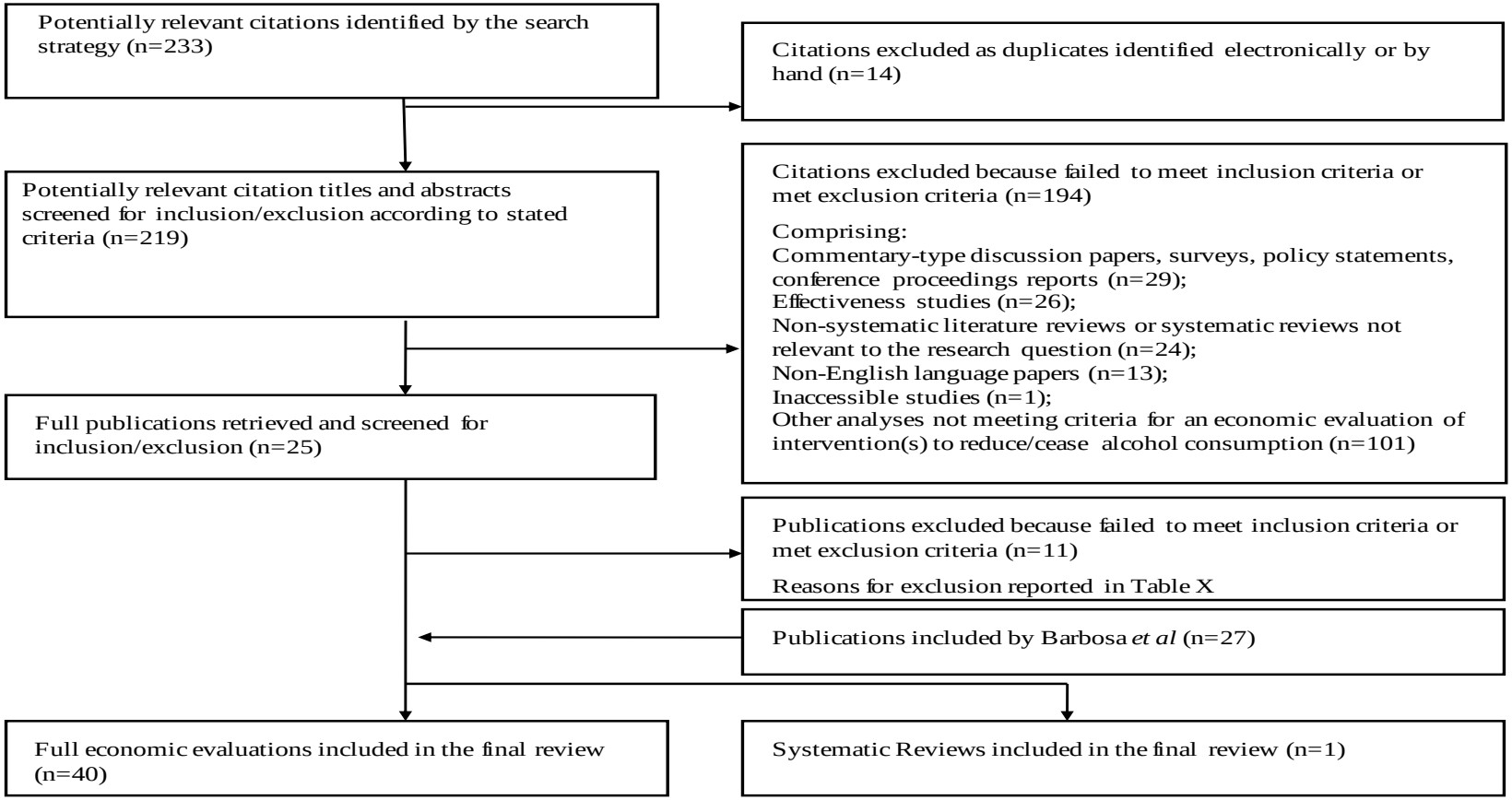
The author extracted data from the full economic evaluation studies included in the final review. Twenty seven full economic evaluations were identified and reviewed by Barbosa *et al* [221-247] and these studies were included in the final review alongside further studies identified by the search. Data extraction tables were identical to those used in the previous chapter and populated using a published checklist for quality appraisal of economic evaluation studies [136]. The results of the systematic review were analysed in a narrative review but not synthesised. Any systematic review studies included in the final review were to be discussed in the narrative review but without data formally extracted, and used to assess the sensitivity of the search strategy, as in Chapter 3.

Quality of economic evaluation studies in the review was appraised using fifteen questions taken from peer reviewed quality appraisal recommendation documents [15, 136].

4.3. Results

Figure 6 comprises the PRISMA flow diagram, describing information about the number of potentially relevant publications identified, included and excluded and aggregate reasons for exclusions [137]. Reasons for exclusions at the final stage, after full publication retrievals, are reported separately in Appendix C, Table 38.

Figure 6: Identification of Studies in the Review



4.3.1. Study Characteristics

Forty full economic evaluations were included in the final review, as shown in Figure 6, and details of key methods and results from these forty studies are reported in Table 36, which is displayed in Appendix C due to its size. None of these studies considered the effect of changing alcohol behaviours upon smoking behaviour, and the associated health and economic consequences. Two studies [248, 249] used data from respective previous studies [228, 247] to perform economic evaluations from alternative viewpoints; these studies are treated as stand-alone studies in this review.

Three of the economic evaluation studies identified by the search strategy were full HTA reports. Two of these reports were recent NICE clinical guideline documents which included CUAs: one estimated the cost-utility of the diagnosis and clinical management of acute alcohol withdrawal patients [250]; the other estimated the cost-utility of adding pharmacological treatment to psychological therapy for individuals in recovery from alcohol dependence [251]. The third HTA identified was a report of the cost-effectiveness of strategies to prevent relapse in alcohol dependent patients from the Health Technology Board for Scotland [252].

Another study identified was a NICE funded investigation into screening and brief intervention for problems linked to excessive alcohol consumption using the Sheffield Alcohol Policy Model (SAPM) [253]. This model was developed by the Sheffield Alcohol Research Group (SARG) at the University of Sheffield to inform a range of alcohol policy questions. The crux of the model links alcohol consumption in an English general population sample to alcohol-related health effects and costs. Using different data to inform the link between policy and alcohol consumption, the SAPM has been used by the SARG to analyse the potential consequences of pricing policies, availability laws and advertising policies, as well as brief interventions aimed at individuals [253].

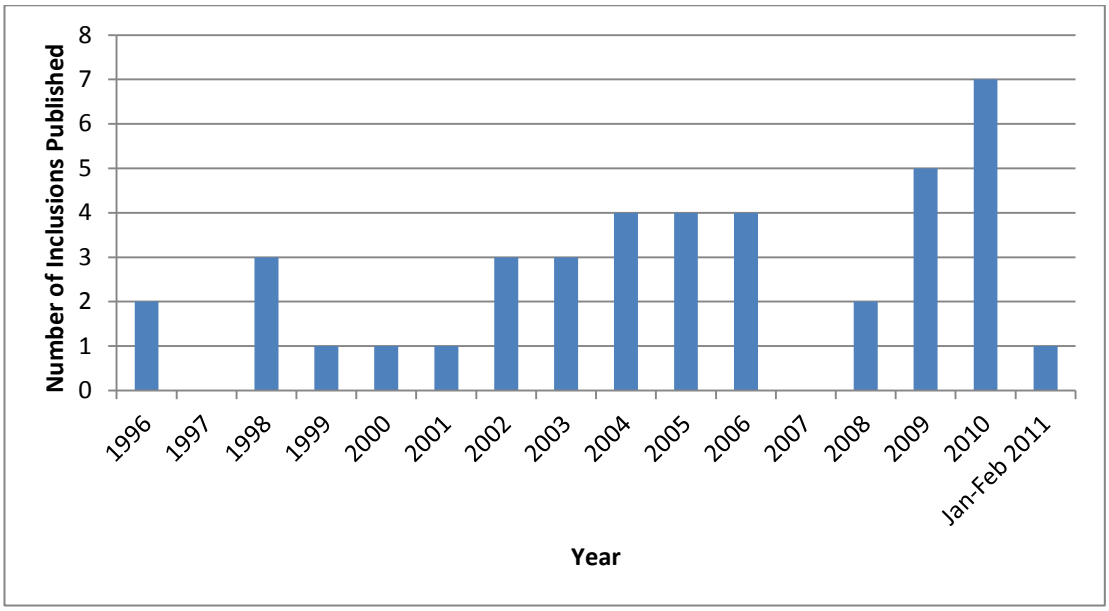
Table 2 and Figure 7 show the distribution of country settings and plot the pattern of publication dates for the forty economic evaluations in the review. There have been fewer publications of economic evaluations of individual level interventions

to change alcohol behaviour than economic evaluations of individual-level interventions to assist smoking cessation, but the patterns of publications across jurisdictions and time hold similar traits. As Table 2 shows, 30% of all inclusions in this review were set in the USA; another 30% were set in the UK. Apart from these, a significant number of studies have been set in Australia. The remainder were conducted using a study population and setting elsewhere in Europe, in Canada or in Brazil. No relevant study set in Africa or Asia was identified. As can be seen in Figure 7, there has been a general rise in the number of economic evaluations published in the area each year over the past fifteen years, peaking in 2010, the last full year recorded. The first economic evaluation of individual level treatment to change alcohol behaviour was published in 1996, a decade after the first economic evaluation of smoking cessation interventions.

Table 2: Country of Setting for Included Economic Evaluation Studies

Setting	**Percentage of Total Inclusions**	**References**
USA	30.0%	[222, 227-231, 237, 240, 247-249, 254]
UK	30.0%	[221, 223, 233, 234, 239, 241, 250-253, 255, 256]
Australia	17.5%	[225, 226, 235, 244, 246, 257, 258]
Germany	10.0%	[224, 238, 242, 243]
France	2.5%	[236]
Holland	2.5%	[259]
Sweden	2.5%	[232]
Canada	2.5%	[245]
Brazil	2.5%	[260]

Figure 7: Number of Included Economic Evaluations Published by Year



Twenty three of the forty economic evaluations in the final review were primary studies [221-224, 227, 228, 230, 231, 233, 234, 236, 237, 239-242, 244, 245, 247, 248, 256, 258, 260]. As the data in Table 36 shows, the primary outcome measure in these studies varied greatly, including: (i) number of days abstinent; (ii) number of drinks per day; (iii) measures of binge drinking. Nineteen of these studies were CEAs [221-224, 227, 230, 231, 233, 234, 236, 237, 240, 242, 244, 245, 247, 248, 258, 260]; the main outcome measure in these studies was in most cases some comparison of primary outcome relative to costs, though several primary CEA studies reported costs and outcomes separately [221, 224, 230, 233, 234, 236, 245]. The three primary CUA studies measured outcome as cost/QALY gained using EQ-5D estimates [239, 241, 256], while the one primary CBA study measured outcome as net monetary benefit to (i) the healthcare payer and (ii) society [228].

The remaining 17 economic evaluations in the final review were modelling studies [225, 226, 229, 232, 235, 238, 243, 246, 249-255, 257, 259]. There was not a single model structure that was used consistently across these studies, though the SAPM model has been used in various applications not separately reviewed here [33, 261-263]. Table 36 shows that the primary measure of effectiveness again varied from study to study, and included: (i) number of days abstinent; (ii) mean alcohol consumption; (iii) measures of binge drinking; (iv) hospital admissions; and (v) drink driving rates. Six of these studies were CEAs and measured outcome as either cost per life year

gained [232, 238, 246] or some comparison of primary outcome relative to costs [226, 243, 252]. The one modelling CBA study in the review used net monetary benefit as the main outcome measure [249]. The majority of modelling studies in the review however, were CUAs, and all bar two CUAs used cost per QALY gained as the main outcome measure; the two remaining CUA studies were set in Australia and used cost per DALY gained [257] and cost per years lived with disability averted [225] as main outcome measures, respectively.

It was again possible to sub-divide the modelling studies by model structure type. No study in the review performed an individual-level analysis; all used cohort model structures. Several studies with short time horizons used untimed decision tree type structures [225, 226, 243, 250-252]; the remainder were timed state-transition models. Unsurprisingly given this lack of model complexity, studies extrapolating to alcohol use in the long-run made simplistic assumptions about long-term alcohol use patterns [232, 235, 238, 246, 252, 253, 255, 257, 259], generally involving a percentage of sustained effect or an assumed relapse rate where drinking states were modelled, as reported in Table 36.

The length of time over which effectiveness was measured also differed across economic evaluations in the review. In all bar one of the twenty three primary studies reviewed effectiveness was measured from intervention until the end of the trial time horizon. The remaining primary study measured effectiveness from 12 months before intervention to the end of the trial time horizon [237]. For twelve of twenty three studies, the time horizon spanned 12 months , but across the remaining eleven primary studies, effectiveness was measured over periods ranging from 12 weeks [231, 258] to 3 years [230, 237]. In the seventeen modelling studies in the review the length of time over which primary effectiveness was measured was not always explicitly reported, as indicated by the absence of such details for respective studies in Table 36. Otherwise, primary effectiveness was measured over 12 months [235, 251, 252, 255, 259], 96 weeks [243] or 3 years [229].

As the primary outcome measure was much varied across the forty economic evaluations in the review, so were the interventions under comparison, and study populations at which these interventions were aimed. Ten studies included one or

more alternative involving pharmacology [238, 242, 243, 247, 248, 250-252, 257, 258] and the drugs administered included acamprosate, naltrexone and disulfiram. These interventions were always targeted at individuals with alcohol dependency, usually newly detoxified. The NICE HTA of treatment regimes for acute alcohol withdrawal was unique within the review in comparing alternatives including oxazepam, chlordiazepoxide, clomethiazole and lorazepam. Three studies compared in-patient detoxification of alcohol dependent patients with some form of alternative detoxification strategy [234, 239, 240], but the majority of studies in Table 36 have compared alternatives involving varying degrees of counselling and personal intervention techniques from health professionals for patients with ranging alcohol problems [222-233, 235, 237, 241, 244, 245, 249, 254-256, 259, 260]. Aside from these, one study has compared different levels of training for health professionals to implement brief interventions [246] and another has compared the impact of the same detoxification regime for alcohol dependent patients across 4 different centres [236].

One trend that is clear from Table 36 is that there is some distinction between the types of treatment aimed at hazardous or harmful drinkers, as defined by their alcohol consumption, and dependent drinkers, often defined by an instrument or tool such as Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria [264]. Thirteen of the forty studies defined their target population by their drinking habits rather than a measure of mental or use disorder [222-224, 226, 228, 232, 245, 246, 249, 253, 255, 256, 259], and the interventions in these studies were typified by some form of motivational or psychological support, and not in-patient or pharmacological treatment.

As in the review of economic evaluations of smoking cessation interventions in the previous chapter, a key difference in costing methods across the modelling studies in this review was whether or not studies included future medical costs alongside intervention costs. Six of the 17 modelling studies in the review included future alcohol-related disease costs in their base case analysis [238, 243, 252, 253, 255, 257]; the alcohol-related diseases considered were wide ranging but not consistent across studies, and included heart disease, stroke, pancreatitis, liver cirrhosis, alcohol dependence syndrome and various cancers. The SAPM considered 47 diseases and

health events linked to alcohol [253], based on extensive research of evidence on harm related to alcohol [265], by far the most extensive battery of diseases and health-related events considered by any study in this review. Two further studies included general future medical costs alongside intervention costs in total cost estimates [232, 259]. Further differences in costing methodologies across studies in the review were consistent with the range of study perspectives employed, as described by the data in Table 36.

4.3.2. Study Findings

As the interventions assessed, measures of effectiveness, and to some extent the specific study populations varied greatly across the forty studies in the review, it was difficult to identify consistent findings. As in Table 33, the optimal alternative in Table 36 is displayed in bold font, where an incremental analysis has been performed. Effectiveness was not always summarised as a rate or odds ratio, and it was difficult to analyse the interaction between effectiveness and economic optimality across studies because of this, and because only fifteen of forty studies were considered to report an incremental analysis [223, 228, 229, 234, 237, 238, 243-245, 249, 251, 253, 254, 258, 260].

Of the thirteen studies that targeted individuals based on their alcohol consumption, only four studies identified economically optimal alternatives after performing incremental analyses [223, 228, 245, 249, 253]. Three of these studies found some form of brief intervention from a health professional preferable to a cheaper alternative such as an information leaflet [223, 228, 249] (though two studies used the same data [228, 249]). Another study found an intervention consisting of information on drinking guidelines to be preferable to motivational enhancement with personalised feedback, because there was no statistically significant difference in effectiveness of the two alternatives [245].

In the studies that assessed one or more alternative involving pharmacology targeted at alcohol dependent patients, regimens of the drugs acamprosate and naltrexone have been found to be effective and cost-effective as respective adjuncts to some kind of psychological care, in maintaining abstinence in newly detoxified alcoholic patients [238, 243, 251, 258]. One study has compared an alternative including naltrexone to an alternative including acamprosate, but did not find

evidence that one drug is more effective than the other in maintaining abstinence [251]. In a study targeting patients seeking help for alcohol problems or categorised as alcohol dependent, outpatient and day programmes for detoxification were generally found to be economically preferable to residential treatment, due mostly to the high intervention costs of the latter [234]. Another study found that personal follow-up care in the form of home visits was an important driver of effectiveness in outpatient detoxification [260].

Of the six modelling studies that included future alcohol-related disease costs in their analyses, in the two studies where effectiveness rates were clearly reported and incremental analysis was performed, the most effective alternative compared favourably with its comparator(s) [243, 252]. However, there was evidence from one study that intervention costs for some alcohol cessation programmes, such as in-patient programmes for alcohol dependents, might be so high that a reduction in long-term costs for more effective interventions would not be enough to justify the initial outlay [257].

4.3.3. Study Quality

The results of the quality appraisal of modelling studies are presented in Table 37 of Appendix C. Overall, the quality of reporting, data identification and analysis was reasonable across the 17 modelling studies, and of a similar standard to the modelling studies reviewed in Chapter 3. Of course, as in Chapter 3, the quality appraisal checklist used does not account for the limitation inherent in cohort state-transition modelling of long-run behavioural patterns. Again, all studies posed a well-defined and answerable research question and reported valid conclusions given the data presented.

The three HTA-type analyses [250-252], the NICE funded analysis using the SAPM [253] and an analysis forming part of a UK PhD thesis [255] were the only studies to use a systematic search and review of evidence to inform model parameters. These studies also generally satisfied more of the fifteen quality criteria than peer-reviewed journal studies.

4.3.4. Search Sensitivity

It was anticipated that the sensitivity of the search strategy used by Barbosa *et al*, and relied upon here, could be assessed by comparing the results of the search to those of other similar searches performed over the same time period. The most recent economic evaluation identified for inclusion in this review was the HTA study comprising part of a NICE guidance document on care for alcohol dependence and harmful alcohol use [251]. The review team searched the databases EMBASE, MEDLINE, HTA, PsycINFO, CINAHL, EconLit and NHS EED to identify economic studies and HTA reports on interventions relevant to care for alcohol use disorders [251]. These searches identified fifteen studies that met the review team's inclusion criteria: two of these studies were published after Barbosa *et al*'s search but identified for inclusion in the updated search performed here [256, 258] . Of the remaining thirteen studies identified by the NICE review team, ten were included in the Barbosa *et al* review and two were cost studies, thus not meeting the inclusion criteria set out by Barbosa *et al*, or stated here. The outstanding study identified by the NICE review team did meet the inclusion criteria for this review, and was identified by this author's search of the HTA database [252].

It should be recognised that as Barbosa *et al* identified and included seventeen economic evaluation studies that were not included in the NICE review [222-226, 228-234, 236, 237, 244-246], it is highly plausible that relevant studies not identified here would not have been included by the NICE review team. However, the results of the NICE review suggest that the search strategy used by Barbosa *et al* was sensitive in general, but insensitive specifically to Health Technology Assessments available directly from individual funding agencies and the HTA database. As the updated search used here anticipated this shortcoming in the Barbosa *et al* search strategy and included an all-years search of the HTA database, the implication is that the search strategy used here was sensitive.

Aside from the systematic review identified in the exploratory search and used to develop the search strategy [218], no further stand alone systematic review of economic evaluations of individual-level interventions to change alcohol behaviour was identified.

4.3.5. Recently Identified Studies

Intermittent citation searches since February 2011 have revealed no significant methodological progress in models for economic appraisals of individual-level strategies for alcohol use behaviour change; no individual-level modelling studies have been identified.

4.4. Discussion

This chapter has reported the results of a systematic review of economic evaluations of alcohol behaviour change interventions aimed at individuals. Only limited data could be found to test the sensitivity of the search, but there is indication that the search strategy was sensitive.

Though not as numerous as economic appraisals of strategies to aid smoking cessation, many economic evaluations have been performed in this area, with a significant number of studies set in the UK, and some indication that the rate of publications in increasing. Still, no study has considered the impact of changing an individual's alcohol behaviour upon their smoking behaviour, and subsequent cost and health consequences.

A significant number of modelling studies were identified, and in many cases these studies extrapolated effects beyond effectiveness data end points. All used cohort models and made simplistic assumptions about behavioural trends in the long-run. In studies assessing treatment options for alcohol dependence, this involved making assumptions about a relapse rate [238, 252, 257]. In studies where consumption among non-dependent drinkers was targeted, assumptions about duration of intervention effect were made [232, 235, 246, 253, 259]. As with long-run smoking patterns in the previous chapter, these assumptions were based on little evidence. Indeed, long-run data on alcohol use patterns is lacking [235, 257]. While important health outcomes depend on behaviour years and decades into the futures, trial follow-up end points are typically much, much shorter. Health economic models to assess strategies to improve drinking behaviour, much like models to appraise smoking cessation strategies, can be improved in the future in two key ways, First, with better data to inform projections of long-term behaviour. Second, with individual-level model structures to allow complex individual-level behaviour to be captured.

Analysis of the longitudinal alcohol use data in HILDA in Chapter 5 will contribute to the existing knowledge about individual-level patterns of alcohol use. What the dataset does not capture though, is information about alcohol use disorders. It is possible to predict alcohol dependency using consumption data, but perhaps the best avenue to improved understanding of long-run behavioural outcomes in alcohol dependence patients is improved trial follow-up. A recent study reported 7-year follow up of 127 alcohol dependence patients [266]. In the future, larger trials with repeated follow-up over this length of time frame or longer should be encouraged to understand long-run behavioural patterns in alcohol dependent patients post treatment.

The health consequences of sustained reductions in alcohol use in the general population are considerable, and the next chapter will help inform the possible long-term consequences of changes in alcohol use. These findings will be primarily useful in informing long-run projections of alcohol use following smoking cessation treatment in the economic appraisal in Chapters 7 and 8, but will also provide evidence for use in future appraisals of individual- level strategies to reduce alcohol consumption. Among reviewed studies targeting behaviour change in drinkers defined by their alcohol consumption, some form of motivational or psychological support was generally found to be effective and cost-effective compared to a less costly alternative, such as information pamphlets.

A key aim of this chapter was to establish methods and data to link alcohol use to health in the *de novo* economic appraisal model described in Chapter 7. As discussed in Chapter 3, NICE methods guidance dictates that relevant long-term costs should be considered in health technology appraisals [6]. Only six of the seventeen modelling studies in the review considered alcohol-related disease costs [238, 243, 252, 253, 255, 257], and the diseases considered varied across these studies. The analysis of the SAPM considered 47 diseases and health events linked to alcohol [253], based on extensive research of evidence on harm related to alcohol [265], by far the most extensive battery of diseases and health-related events considered by any study in this review. The data and methods employed to link alcohol use to health effects in this study were the most thorough and appropriate for use in this project.

4.5. Chapter Summary

The discussion points raised by the review presented in this chapter have mirrored those of Chapter 3. Forty relevant economic appraisal studies were identified, yet none have considered the link between alcohol and tobacco use. Modelling techniques have been used to extrapolate beyond trial end points and incorporate long-run consequences of changes to alcohol behaviour. Cohort model structures have been used consistently, and this along with data limitations has led to various unrealistic assumptions about long-run behaviour which may have influenced results. Nevertheless, methods and data to link alcohol use to health in Chapters 7 and 8 have been identified in a recent application of the SAPM [253].

Overall, Chapters 3 and 4 have shown that while the economics of strategies for smoking cessation and alcohol reduction are not under-researched areas, existing studies have generally used cohort analyses, when individual-level modelling is a far more suitable approach to capture the complexity of these behaviours. Chapters 2, 3 and 4 have together highlighted a narrative of limited knowledge about long-run patterns of smoking and drinking behaviour. Next, Chapter 5 aims to contribute evidence in this area, for use in economic appraisal models and elsewhere, with analysis of HILDA data.

5. Chapter 5: The Dynamics and Interdependency of Smoking Status and Alcohol Use: Evidence from HILDA

5.1. Introduction

Chapter 2 presented existing evidence that smoking and alcohol use are related behaviours. Chapters 3 and 4 underlined that economic appraisals of strategies to influence smoking or alcohol use in individuals have not considered the implications of such a link. Together, Chapters 2, 3 and 4 have highlighted the lack of analyses on the long-run link between alcohol use and smoking, but also the probable lack of analyses of long-run patterns of behaviour for each separately. Longitudinal survey data offer an opportunity to estimate causal behavioural relationships and produce evidence on the interrelated and dynamic natures of alcohol use and smoking, in a form that is useful to better inform assumptions about long-run behaviour in future economic appraisals. A key aim of Chapter 5 is to generate such evidence for use in economic models.

The analysis uses nine waves of data from HILDA. HILDA contains rich longitudinal individual-level data on alcohol and tobacco use, as well as a range of important socio-economic confounding factors, and represents the best available data source [111]. The core analysis jointly estimates the dynamics of tobacco and alcohol use.

Chapter 5 is structured as follows. Section 5.2 reviews existing studies which have aimed to estimate links between alcohol use and smoking. Section 5.3 then describes the rational addiction theoretical framework underpinning the analysis. Section 5.4 sets out the econometric framework and estimation procedure. Section 5.5 briefly recounts the characteristics of HILDA and describes the variables employed in the analysis. Section 5.6 presents model results. Section 5.7 then sets out how these results can be used to project long-term behaviour in economic appraisal models. Finally, Section 5.8 then discusses and evaluates the results, with consideration of their usefulness and various limitations for the purpose of this thesis and elsewhere, before the chapter is summarised.

5.2. Literature Review

An exploratory search for existing econometric analyses estimating links between smoking and drinking using individual-level data was performed using the database Econlit (via Ovid). The initial search comprised the following: [(alcohol$) and [(tobac$ or cigaret$ or smok$)]]. Following this search, citation searches using key identified studies were intermittently performed. The studies found varied in terms of questions addressed, data and methodology.

Only one study used panel data with individual-level socioeconomic information to estimate the relationship between tobacco behaviour and alcohol behaviour. Picone *et al* took advantage of a natural experiment in the form of public smoking bans and price increases across American states to test the impact of tobacco policy upon alcohol consumption in their 2004 publication [267]. Data from the first six waves of the Health and Retirement Survey (HRS), a health and socio-demographic panel survey beginning in 1992 with a sample of individuals aged 51 to 61 years, with successive waves every two years, was supplemented with price data on alcohol and cigarettes [267].

Picone *et al* based their econometric strategy upon a rational addiction theoretical framework, described further in Section 5.2, whereby individuals maximise their utility by consuming addictive goods (tobacco and alcohol) and non-addictive goods subject to a budget constraint [267]. Assuming a quadratic utility function, the authors derived reduced-form equations for tobacco and alcohol consumption:

$$y_{1it} = \gamma_{11} y_{1i\,t-1} + \gamma_{12} y_{2i\,t-1} + \beta_{11} P_{iy1t} + \beta_{12} P_{iy2t} + \beta_{13} P_{iZt} + \beta_{14} X_{it} + v_{1i} + u_{1it} \quad (4)$$

$$y_{2it} = \gamma_{21} y_{1i\,t-1} + \gamma_{22} y_{2i\,t-1} + \beta_{21} P_{iy1t} + \beta_{22} P_{iy2t} + \beta_{23} P_{iZt} + \beta_{24} X_{it} + v_{2i} + u_{2it} \quad (5)$$

In equations (4) and (5), y_{1it} and y_{2it} are respective tobacco and alcohol consumption for individual *i* at time *t*, X_{it} is a vector of observable determinants of alcohol and tobacco consumption, Z_t is the composite of non-addictive goods in

time t and P_{iy1t}, P_{iy2t} and P_{iZt} are the prices of A, T and Z that individual i faces at time t. Time-invariant unobservable individual factors that influence tobacco and alcohol consumption, such as personal taste, are modelled by v_{1i} and v_{2i}, respectively, while u_{1it} and u_{2it} are respective error terms for the two equations.

Econometric models such as that estimated by Picone *et al* are useful if their parameter estimates have causal interpretation. In simple terms, the causal effect of a change in an explanatory variable upon the outcome in an econometric equation is measured by some transformation of its parameter value, when all other explanatory variables in the model (observed and unobserved) are held constant [268]. Causal interpretation is not achievable when it is impossible to change an explanatory variable while holding all other explanatory factors constant. This is the case when observed explanatory variables are correlated with unobserved explanatory variables, which in Picone et al's specification comprise the time-invariant unobservable effects v_{1i} and v_{2i} and the time-variant errors u_{1it} and u_{2it}. In econometric models, explanatory variables are described as *exogenous* when they are uncorrelated with the unobserved explanatory variable(s) (and *endogenous* when they are not) [268].

Picone *et al* recognised that unobserved preferences for tobacco (alcohol) are correlated with $y_{1i\,t-1}$ and likely $y_{2i\,t-1}$ in equation (4) ($y_{2i\,t-1}$ and likely $y_{1i\,t-1}$ in equation (5)), and used a first-differences transformation (removing all variation between observations at the same time-point to leave only 'within' variation) to eliminate v_{1i} and v_{2i}.

Recognising that lagged first differences in tobacco and alcohol were potentially correlated with the transformed error terms, the strategy was then to find a set of *instrumental variables* for $\Delta y_{1i\,t-1}$ and $\Delta y_{2i\,t-1}$ (uncorrelated with Δu_{1it} and Δu_{2it}) [267]. Instrumental variables can be useful when causality cannot be established. Essentially, observable variables correlated with endogenous variables, but uncorrelated with other variables in the model, act as 'instruments' for the endogenous variables. The instruments used by Picone *et al* were taken from lagged levels of y_{1it} and y_{2it} and lagged differences in prices.

Picone *et al* estimated equations (4) and (5) separately, for male and female sub-samples [267]. Results showed instrumented lagged smoking and drinking to have a modest and not always significant effect upon alcohol and tobacco consumption. The reinforcement effect of past cigarette consumption upon present cigarette consumption was more important than the cross-behaviour effect of past alcohol consumption, and similarly past alcohol use was more important than past smoking in explaining current alcohol consumption. Increasing the price of cigarettes was shown to increase alcohol consumption, while smoking bans appeared to lead to reduced consumption of alcohol among females. Taken at face value, this implies that cigarettes and alcohol are both complements and substitutes in consumption: potentially contradictory results. However, price increases and clean air laws are clearly different types of policies, and are difficult to compare. Picone *et al* argued that these results could reflect different consumer types responding to price increases and physical smoking restrictions in different ways: for those who primarily drink alcohol socially, at pubs and bars, cigarettes are a complement to alcohol, whereas for those who drink primarily to relieve stress, cigarettes act as a substitute [267]. Though speculative, this argument correctly highlights that the relationship between alcohol behaviours and cigarette behaviours may be different for different sub-groups.

Overall, the work of Picone *et al* has been most useful in underlining the importance of addiction and difficulty of addressing the problem of endogeneity in modelling the dynamic links between alcohol and tobacco use. However, by eliminating unobserved time-invariant effects in their approach, and estimating equations separately, Picone and colleagues were then not able to quantify the correlation between preferences for alcohol and tobacco use; something that would be a useful addition to the literature.

No further relevant analyses have employed panel data. Goodman used data from the 2001-2002 NESARC, a familiar dataset from the brief review in Chapter 2, to estimate the determinants of alcohol, tobacco and unspecified illicit drug participation [269]. Goodman was interested in the endogenous nature of these decisions, and modelled the joint participation decisions using a multinomial logit model [269].

Briefly, a logit model could be described by equation (6):

$$y^* = X'\beta + u \quad (6)$$

$$y = 1 \; if \; y^* > 0$$

$$y = 0 \; if \; y^* \leq 0$$

Where y^* is a latent variable, X is a vector of exogenous explanatory variables and u has a mean value of zero and is assumed to follow a logistic distribution [96]. The logit model (and equally the probit model, which differs in that it imposes a normality assumption on the distribution of the error term) is thus useful in estimating the determinants of a binary variable, such as the decision of whether to participate in an activity or behaviour.

The logit model extends to the unordered multinomial logit model when the dependent variable constitutes a single choice between J unordered alternatives. It is possible to describe such a multinomial logit model by the following equation [96]:

$$Prob(y_i = j) = \frac{e^{\beta' j X_i}}{\sum_{k=0}^{J} e^{\beta' k X_i}} \quad (7)$$

$$j = 0,1, \ldots, J; \quad k \neq j$$

In the context of Goodman's model, the dependent variable comprised eight alternatives (J=7 in equation (7)) with corresponding probabilities, from not participating in alcohol, cigarettes or drug use, to participating in all three behaviours.

Consistent estimation of the multinomial logit model parameters by maximum likelihood is reliant on the condition that the odds ratios are independent of alternatives in the model [96]; this condition is known as independence from irrelevant alternatives (IIA) [96]. IIA imposes that the probability of choosing between two alternatives should not be affected by the addition of a third alternative. IIA is a helpful assumption for estimation, but is fallible in the context

of many real-world multiple-choice problems. Goodman tested the assumption of IIA by testing whether the parameter estimates systematically change when supposedly irrelevant choices are omitted from the model. In doing so, Goodman tested the impact of (i) adding the choice of recreational drugs participation to the tobacco and alcohol choices; (ii) adding the choice of alcohol to the tobacco and drugs choices; (iii) adding the choice of tobacco to the alcohol and drugs choices; using Chi-squared statistics [269]. The results of Goodman's tests generally support the assumption of IIA, but the tests performed were not comprehensive. Goodman did not test the assumption of IIA in the context of adding the option of tobacco and alcohol participation jointly to the choice between alcohol participation only and tobacco participation only, or adding the option of participating in drugs, alcohol and tobacco jointly to the options of participating in drugs and alcohol jointly or participating in alcohol and tobacco jointly.

Higher cigarette taxes were found to be correlated with slightly higher probabilities of drinking, leading the author to conclude that a mild substitution effect was present [269], an unexpected result in the context of the wider literature encountered in earlier chapters. Estimation of the multinomial logit model is fairly straightforward, and so the approach is appealing, but the assumption of IIA may not be realistic, and so the parameter estimates presented by Goodman may not be the most efficient.

Zhao and Harris investigated a similar research question to Goodman [269], aiming to understand the determinants of alcohol, tobacco and marijuana participation (and consumption), but in the context of correlation between behavioural choices [270]. Pooled cross-sections of Australian National Drug Strategy Household Survey (NDSHS) data on alcohol, tobacco and drug use and various socio-economic factors, from over 40,000 individuals, were employed alongside regional price data [270].

The econometric model employed was the multivariate probit (MVP) model [270]. Equation (6) described the probit/logit model. An MVP model can be described as a system of probit equations [271], where error terms have a joint distribution [96]. Equations (8) and (9), below, describe the MVP model estimated by Zhao and

Harris, where y_A^*, y_T^* and y_M^* are underlying propensities to partake in alcohol, tobacco and marijuana, respectively [270, 271]:

$$y_A^* = X_A\beta_A + u_A \quad (8)$$
$$y_T^* = X_T\beta_T + u_T$$
$$y_M^* = X_M\beta_M + u_M$$

$$y_A = 1 \; if \; y_A^* > 0, \;\; y_A = 0 \; otherwise$$
$$y_T = 1 \; if \; y_T^* > 0, \;\; y_T = 0 \; otherwise$$
$$y_M = 1 \; if \; y_M^* > 0, \;\; y_M = 0 \; otherwise$$

$$\begin{pmatrix} u_A \\ u_T \\ u_M \end{pmatrix} \sim N\left\{ \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 1 & \rho_{TA} & \rho_{MA} \\ \rho_{AT} & 1 & \rho_{MT} \\ \rho_{AM} & \rho_{TM} & 1 \end{bmatrix} \right\} \quad (9)$$

It is not possible to identify the size of the variance of errors in equations in the multivariate probit model, so Zhao and Harris assumed unity, as shown in covariance matrix (9). Crucially, the explanatory variables in X_A, X_T and X_M include prices for the three addictive goods, but not the other dependent variables, and were assumed to be exogenous. As such, the MVP model offered efficiency gains to Zhao and Harris compared to three separate probit models, assuming a joint distribution of error terms, but was bound to produce identical mean parameter estimates.

Probit models require maximum likelihood (ML) estimation. Estimation of the log-likelihood function for the MVP model though is made complicated by the presence of multiple integrals [272]. A technique called *maximum simulated likelihood* (MSL) was employed by Zhao and Harris for estimation [270], whereby probabilities to enter the log-likelihood were simulated using the 'GHK' algorithm, named after the authors who independently developed the method to simulate these probabilities [272, 273].

The covariance parameters in (9) estimated by Zhao and Harris are positive and highly statistically significant [270], indicating that the three participation decisions

are positively correlated and that the joint specification was justified on the grounds of efficiency. Other results showed a percentage increase in the price of alcohol to significantly reduce the probability of tobacco participation, and similarly a percentage increase in tobacco price significantly to reduce the probability of drinking [270]. Thus the authors drew the conclusion that alcohol and tobacco are complements in participation [270], in contrast to Goodman's findings [269].

The key criticism of both the MVP model estimated by Zhao and Harris and the multinomial logit model estimated by Goodman, relates to the use of cross-sectional data. Picone *et al* recognised that alcohol and tobacco are addictive goods; past behaviour is highly predictive of current and future behaviour. Without observing past behaviour, the models of Zhao and Harris and Goodman lack explanatory power. Further than this though, their parameter estimates are potentially inconsistent. The influence of addiction and past behaviour upon current behaviour is unobserved in static models. If this unobserved influence is correlated with observed explanatory variables, corresponding parameter estimates will contain bias. Extension of the MVP model proposed by Zhao and Harris to the dynamic case would be a marked improvement, and possible with data such as those available in HILDA.

Recognising that the participation decisions for alcohol, tobacco and marijuana are different to the consumption decisions, Zhao and Harris did extend their analysis to estimate the determinants of consumption of the three substances [270]. This is important: the decision to smoke (the participation decision) and the choice of how much to smoke (the consumption decision) are distinct but possibly related mechanisms and should be treated as such. A study of the determinants of cigarette demand using detailed primary data from Greece has in fact found evidence that the determinants of smoking participation are not necessarily analogous to the determinants of cigarette consumption [274].

In order to specify consumption equations, Zhao and Harris employed the ordered probit model [270]. The ordered probit generalises the concept of the latent-variable approach of the probit model to the notion of multiple, ordered thresholds

[271]. This approach is useful when the dependent variable has numerous categorical choices which are ordinal in nature. Zhao and Harris viewed the decision over consumption, among participants in each behaviour, as a decision between ordered categories [270]. The alcohol and tobacco consumption decisions were each modelled as equations with three categories in the dependent variables, ranging from low consumption to high consumption. As such, the ordered probit model for the alcohol consumption decision can be described by equation (10), where K_1 and K_2 were threshold values between the three consumption categories:

$$y^* = X'\beta + u \qquad (10)$$

$$y = 0 \; if \; y^* \leq K_1$$

$$y = 1 \; if \; K_1 < y^* \leq K_2$$

$$y = 2 \; if \; K_2 < y^*$$

Cross-price results from estimation of the ordered probit equations showed alcohol and tobacco to be complements in consumption as well as participation [270].

Other econometric analyses have used individual-level data supplemented by price data to estimate the relationship between tobacco and alcohol behaviours [275-277]. In each of these studies cross-sectional data [276] or pooled cross-sections of individual-level surveys [275, 277] were combined with aggregate price data. Two sets of authors, Decker and Schwartz [275] and Jimenez and Labeaga [276], estimated consumption equations, but all three studies estimated separate participation equations to determine interdependencies.

The results from two of the three studies indicated negative cross-price effects between alcohol and cigarettes, suggesting complementarity [276, 277]. In the remaining study, Decker and Schwartz found a positive cross-price effect, suggesting that alcohol and cigarettes are substitutes in consumption [275]. The authors also found that while a rise in alcohol price decreased cigarette participation, an increase in the price of cigarettes increased alcohol participation

[275]. This suggests the plausible possibility that individuals smoke because they drink, but do not drink because they smoke.

However, as well as relying on cross-price effects for inference about inter-behavioural relationships in the absence of longitudinal individual-level data, these studies have been criticised for attempting to marry individual-level consumer data with aggregate price data [278]. Tauchmann *et al* highlight that as prices are not consumer-specific, such analyses are reliant on limited price variation across periods and/or across regions for explanatory power [278].

Tauchmann *et al* reject cross-price elasticity of demand estimates in favour of expressing alcohol (tobacco) consumption as a function of tobacco (alcohol) consumption and explanatory variables, and attempt to capture price effects by including dummy variables for regional and time effects [278]. Due to concerns over endogeneity in their reduced form estimation equations, tobacco consumption and alcohol consumption were instrumented by parental tobacco consumption and parental alcohol consumption, respectively, in Tauchmann *et al*'s analysis. Tauchmann *et al*'s approach, therefore, relied on the assumption that parental smoking (drinking) does not affect an individual's drinking (smoking), except through their own smoking (drinking) habits [278].

The dataset employed comprised consecutive cross sections of individual-level non-panel data and reduced form equations for consumption were modelled as Tobit models [278]. The Tobit model is similar to the probit model when the dependent variable is continuous but limited at zero, and therefore useful for applications such as alcohol and tobacco consumption. The following equation describes a simple Tobit model:

$$y^* = X\beta + u \qquad (11)$$

$$y = y^* \; if \; y^* > 0,$$

$$y = 0 \; if \; y^* \leq 0$$

Where y^* is a latent variable and the error term follows a normal distribution. The estimation results found smoking to positively impact the propensity to drink, leading the authors to conclude that alcohol and tobacco are complements [278].

Other studies have retrospectively analysed the effects of legislative changes on individual-level behaviour, to make some inference about the relationship between alcohol and tobacco use. Over the last ten years, in the UK and many other countries, smoking cigarettes has become illegal in public places, including public houses, bars and restaurants. If comprehensive smoking bans lead to smoking cessation, analysing the impact of a smoking ban upon subsequent alcohol use could provide insight. Several American studies have tested the effect on bar sales or staffing levels of state-level smoking bans, but while some studies have found smoking bans to have a negative effect upon the hospitality industry [279-282], others have found that staffing levels and revenue actually increased following a ban [283-286]. These studies though cannot account for the possibility that individuals change their drinking habits away from bars and restaurants following a ban.

Fewer studies have tried to assess the impact of smoking restriction laws on overall alcohol use. Picone *et al*, discussed above, found evidence of reduced alcohol consumption following a smoking ban [267]. Hyland *et al* used a cross-country comparison between The Republic of Ireland, Scotland and the rest of the UK to assess whether smoking bans are associated with more drinking inside the home [287]. The authors employed ITC study telephone interview data, collected in February and March 2006; after the March 2004 Republic of Ireland smoking ban, but before bans in England (1st July 2007), Scotland (26th March 2006), Wales (2nd April 2007) and Northern Ireland (30th April 2007). The findings showed a lower percentage of alcoholic drinks consumed in the home in the Republic of Ireland compared to Scotland and the rest of the United Kingdom [287], supporting a hypothesis that smoking bans lead to an average reduction in overall drinking. These findings of course rest on the assumption that cultural differences in drinking habits were not important. Elsewhere, changes in the proportion of total alcohol consumption taking place in pubs and restaurants after a smoking ban have been analysed using bimonthly Norwegian data, but no long-term effect was found [288]. Overall, the limited evidence available suggests that public smoking restrictions have had either a neutral or reducing effect upon drinking at home.

The picture emerging from this part of the literature is blurred, but suggests that smoking bans may lead to an overall reduction in alcohol consumption: suggesting

complementarity between alcohol and tobacco. However, it is important to consider that the scope of this PhD research is defined as assessing the effect of individual-level interventions to change behaviour. A smoking ban is only relevant here as a treatment to the extent that it can be used as an instrument for an individual-level smoking cessation strategy. If smoking bans influence alcohol use, the effect may be very different to that of an individual behavioural and drug-based intervention for smoking cessation.

5.2.1. Literature Review Conclusions

Panel data have clear advantages over cross-sectional data for modelling links between alcohol use and tobacco use, particularly given that these are addictive behaviours. Nonetheless, only one study has used individual-level panel data to model alcohol and tobacco use as dynamic processes [267]. This could reflect paucity of suitable data, but such data are available in the HILDA dataset. Further analysis of the dynamic and potentially interrelated processes of alcohol and tobacco use is needed, and can be used to inform economic appraisals of behaviour change strategies for alcohol and tobacco use.

Existing study methods have been useful in consideration of appropriate methodology for analysis of HILDA data. Results from Picone *et al* suggest that past use is highly predictive of current use for both alcohol and tobacco consumption [267], while Zhao and Harris have highlighted the potential importance of a multivariate specification if error terms across alcohol and tobacco use equations are jointly distributed [270]. The majority of studies have used price-elasticity estimates to capture the link between tobacco and alcohol use [267, 269, 270, 275-277, 289-293]. This has though led to conflicting results across studies with regards to whether alcohol and tobacco goods are complements or substitutes. One author has suggested that because prices are aggregated, inference in these studies relies on limited price variation across periods and/or across regions [278]. Price variation is undoubtedly important in influencing tobacco and alcohol use, and price elasticities are useful tools for inference. Similarly, analyses of the effect of clean air laws upon alcohol use are of interest in this area. However, use of alcohol and tobacco is linked in ways that will not be captured in cross-price effects or by the influence of smoking restrictions on alcohol use. When the interest is in

informing potential cross-behaviour consequences of smoking cessation treatment, or a brief intervention to reduce alcohol consumption, these tools are less appropriate.

Where studies have looked beyond price and policy effects to capture a quantitative link between alcohol use and smoking, instrumental variables have been used to overcome endogeneity issues when trying to interpret alcohol (tobacco) use as a function of tobacco (alcohol) use [278, 294]. This approach has drawbacks though, most notably the difficulty of finding appropriate instruments.

Other important issues raised in this review include the differences between decisions relating to alcohol use and smoking. For both, the decision to participate is different to the decision over how much to consume, and may have different determinants. With reference to the behaviour change strategies appraised in Chapters 3 and 4, the participation decision is of most interest in terms of smoking behaviour, where smoking cessation is targeted, whereas reductions in consumption of alcohol in those at-risk of health consequences are the general aims of interventions to influence alcohol behaviour. It has also been highlighted that the link between behaviours may vary between sub-groups of individuals. These are important factors to consider for the analysis of HILDA.

With knowledge from existing work in mind, the next section sets out the theoretical framework for a dynamic and bivariate model to analyse alcohol and tobacco use behaviours using data from HILDA.

5.3. Theoretical Framework

Demand in the context of addictive goods has been investigated in the field of economics since the early decades of the twentieth century [295, 296], and it is in the economic theories of addictive consumption that this analysis lays its theoretical grounding.

Chaloupka and Warner have outlined three separable groups of economic models of addiction: imperfectly rational models of addictive behaviour; models of myopic addictive behaviour; and models of rational addictive behaviour [295]. The first model is characterised by inconsistent short-term and long-term preferences within individuals, so that the short-sighted part of an individual that wants

present satisfaction from addictive behaviour battles with the long-sighted part that wants to avoid the long-run negative consequences of addictive behaviour. However, empirical applications to test the imperfect rational addiction model of health behaviour are lacking [295].

In myopic addiction models, individuals recognise the implications of past consumption behaviour on present consumption, but ignore the impact of past and present consumption on future consumption decisions when making current choices [295]. By contrast, in rational addiction models individuals incorporate the interdependence between past, present and future addictive consumption into the consumption decision to maximise lifetime utility [295]. Though not the first, perhaps the most famous model of rational addiction is that proposed by Becker and Murphy in 1988 [297]. The authors derived several hypotheses from the basic theory of forward-looking rational addiction, including 'adjacent complementarity': an increase in current consumption of an addictive good will increase future consumption of the good for an individual [297].

There has been criticism of forward-looking models of addiction. Akerlof has argued that since smokers are fully aware of the future consequences of initiation and continuation of smoking when these decisions are made, there should never be individuals in the rational addiction model of smoking who regret past decisions [298]. However, there is clear evidence of regret about the decision to start smoking among the majority of smokers from a selection of countries worldwide [299]. Far from being fully aware, adolescent and adult smokers have been shown to underestimate personal risk from smoking in several studies [300-302]. As later noted [303], this apparent inconsistency could also be explained by the potential relationship between addiction and time preferences within the framework of rational addiction. The rational addiction model from Becker and Murphy implied that people who discount the future more heavily have a greater chance of addiction [297, 303]; regret at later time periods could be totally explained by high discounting of time. When the future is discounted heavily, the rational addiction framework reduces to the myopic addiction framework.

Myopic and rational addiction models have been tested empirically, with specific applications to tobacco and alcohol demand, separately. Demand for cigarettes was shown to be a function of a 'stock of past habits' using aggregate US and Western European data [304] and using American survey data [305], supporting the myopic model of addiction, but elsewhere alternative US survey data was used to show that while smoking is an addictive behaviour, smokers do not behave myopically [306]. Analysis of aggregate panel data from forty-two US states over thirty-five years has shown the rational addiction framework to be consistent with the demand for alcohol [307]. Elsewhere, the assumption imbedded in the full rational addiction model that future consequences of addictive behaviours are known and understood has been tested and shown to be weak [300-302].

The literature review demonstrated that a myopic addiction framework has been extended to analyse interactions between smoking and drinking [267]. For the purpose of informing assumptions about long-run behaviour in economic appraisals, the full rational addiction model is impractical. The model developed here will be used to predict behaviour based on individual-level characteristics and past behaviour, which are known. It is not possible to predict behaviour based on behaviour further in the future, which is unknown. A myopic addiction framework is the basis for this analysis.

The initial myopic co-addiction framework outlined here is similar to that used by Picone *et al* [267]. Individuals within the framework aim to maximise their utility subject to a finite budget constraint, as follows:

$$Max_{y_{1t},y_{2t},Z_t}\, U(y_{1t}, y_{2t}, Z_t \mid y_{1\,t-1}, y_{2\,t-1}) \quad subject\ to \quad W_t = P_{y1t}y_{1t} + P_{y2t}y_{2t} + P_{Zt}Z_t \qquad (13)$$

In this equation, y_{1t} and y_{2t} are respective tobacco and alcohol consumption for each individual. Z_t is the composite of non-addictive goods in time t and W_t is monetary income in t that is exhausted by consumption of y_1, y_2 and Z in t. P_{y1t}, P_{y2t} and P_{Zt} are prices for y_1, y_2 and Z in t.

A standard assumption used in the literature to derive demand equations from this constrained optimisation problem is a quadratic utility function [291]. Taking this approach, the following reduced form equations for alcohol and tobacco demand for the *i*th individual are derived:

$$y_{1it} = \gamma_{11} y_{1i\,t-1} + \gamma_{12} y_{2i\,t-1} + \beta_{11} P_{iy1t} + \beta_{12} P_{iy2t} + \beta_{13} P_{iZt} + \beta_{14} X_{it} + v_{1i} + u_{1it} \quad (14)$$

$$y_{2it} = \gamma_{21} y_{1i\,t-1} + \gamma_{22} y_{2i\,t-1} + \beta_{21} P_{iy1t} + \beta_{22} P_{iy2t} + \beta_{23} P_{iZt} + \beta_{24} X_{it} + v_{2i} + u_{2it} \quad (15)$$

In equations (14) and (15), as in equations (4) and (5), X_{it} is a time-varying vector of observable determinants of alcohol and tobacco consumption, v_{ji} , $j = 1{,}2$ are unobserved time-invariant individual effects and u_{jit} , $j = 1{,}2$ are error terms [2].

At this point, this chapter deviates from the work of Picone *et al* in two key ways. Firstly, the dependent variables y_{1it} and y_{2it} are binary. The variable y_{1it} takes on a value of 1 for smokers and 0 for non-smokers; the variable y_{2it} takes on a value of 1 when alcohol consumption is above government recommended alcohol consumption thresholds, or 'at-risk', and 0 otherwise. As has been reported within this thesis, there is no healthy smoking level, and policy has thus targeted reducing the prevalence of smoking, through cessation support for current smokers among other strategies. By contrast, drinking alcohol at low levels is not thought to pose a significant health risk, and policy has generally targeted reducing alcohol consumption below health-risk thresholds, in non alcohol-dependent populations. Consumption is more naturally modelled as a continuous variable and the choice to categorise consumption into two groups was made for two reasons. First, self reported alcohol use data is prone to inaccuracy [308]. If an individual reports drinking 10 UK units of alcohol weekly one year and 30 units weekly the next year, the actual increase in consumption might not be 20 units, but one can be more

[2] Observable determinants of y_1 and y_2 may differ

confident that the individual has moved from a safe to an unhealthy level of consumption. Second, a computer programme to estimate parameters for a useful and appropriate model which treats the dependent variables as binary was available from the literature. This programme is described in more detail below.

Given resource constraints, it was not possible to develop a *de novo* programme to estimate parameters for a model treating the dependent variables differently. It is recognised that treating y_{2it} as a binary variable is a limitation, in that the influence of very heavy drinking upon propensity to smoke might be greater than the influence of a drinking level just above the guideline threshold, and this analysis cannot capture such differences. This limitation is also of consequence for the way alcohol use is modelled in the BIT model in Chapters 7 and 8. To expand, if a patient in the model is predicted to be an 'at-risk' drinker at a point in time, their risk of alcohol related disease is estimated using equations linking alcohol consumption to health events. Having to make an assumption about where this individual's consumption lies in the distribution of at-risk drinkers means that their consumption will very likely be either under- or over-estimated, but it is assumed that little bias will result. The distinction between drinking above guideline consumption levels and below is useful for both (i) differences in the link to smoking and (ii) consequences for health.

The other way in which this work deviates from that of Picone *et al* is that equations are jointly estimated. This marks a potential improvement on existing work in the area. These specific issues, alongside other econometrics issues, are described and analysed below. First, the characteristics of the HILDA dataset are recounted and variables employed in the analysis described.

5.4. Data

5.4.1. The HILDA dataset

The HILDA dataset was established in Chapter 2 as the best available data source for analysis of the interrelated dynamics of smoking and alcohol use. This chapter utilises waves 2 to 10 of the dataset, with the omission of wave 1 data explained by the highly limited alcohol data available in the original survey. The variables used are described in this subsection.

5.4.2. Variables

Descriptive statistics of the key variables in the HILDA dataset are reported in Table 3. Section 5.4.2 serves describes these variables.

Table 3: Descriptive statistics; Full, unweighted, unbalanced sample

Variable	Observations	Mean	Standard Deviation	Minimum	Maximum
Smoker	98447	0.21	0.41	0	1
At-risk Drinker	97890	0.16	0.37	0	1
Smoker last year	80250	0.21	0.41	0	1
At-risk Drinker last year	79839	0.16	0.37	0	1
Age	152517	35.90	22.60	0	93
Male	152517	0.50	0.50	0	1
Divorced	110707	0.09	0.29	0	1
Widowed	110707	0.06	0.23	0	1
Separated	110707	0.03	0.18	0	1
Never married, cohabiting	110707	0.09	0.28	0	1
Never married, not cohabiting	110707	0.24	0.43	0	1
Married (reference category)	110707	0.49	0.50	0	1
Child(ren) residing at family home	110735	0.36	0.48	0	1
Graduate Education	110686	0.20	0.40	0	1
Vocational Further Education	110686	0.30	0.46	0	1
Secondary or No Education (reference category)	110735	0.50	0.50	0	1
Price Index Tobacco	152513	121.49	19.53	100	175.47
Price Index Alcohol	152513	114.55	10.59	100	137.68
Natural logarithm of Household Annual Disposable Income	152517	10.89	0.88	0	14.51

Variable	Observations	Mean	Standard Deviation	Minimum	Maximum
Poor Health	97959	0.03	0.18	0	1
Fair Health	97959	0.14	0.35	0	1
Good Health	97959	0.36	0.48	0	1
Very good or Excellent Health (reference category)	97959	0.47	0.50	0	1
Smoking Ban	152517	0.46	0.50	0	1
Major City Residence	155430	0.56	0.50	0	1

As described previously, binary variables are used to model tobacco- and alcohol-related behaviour. The UK Government daily guideline for safe drinking is no more than 2 to 3 units of alcohol for women and no more than 3 to 4 units for men [309]. Accordingly, 'hazardous' drinking has been defined by Purshouse *et al* as 14 to 34 units in a week for women and 21 to 49 units in a week for men in a recent UK study, while the more consequential 'heavy' drinking was defined as at least 35 units per week for women and at least 50 units per week for men [253]. This classification leads to a convenient binary categorisation of 'hazardous/heavy' drinking, as opposed to non-'hazardous/heavy' drinking, to describe 'risky' alcohol behaviours in contrast to 'non-risky' alcohol behaviours. For ease of reference and consistency, 'hazardous/heavy' is termed 'at-risk' throughout this thesis.

In each of the ten waves of HILDA since and including the first wave of data in 2001, respondents have been asked details concerning their drinking behaviour [310]. In 2001, all respondents eligible to complete the Self-Completion Questionnaire, comprising all those aged 16 years and older, were asked 'How often do you drink alcohol?'. This question was changed in 2002 and for all subsequent waves to 'Do you drink alcohol?', with eight possible responses: **1**. *I have never drunk alcohol*; **2**. *I no longer drink*; **3**. *Yes, I drink alcohol everyday*; **4**. *Yes, I drink alcohol 5 or 6 days per week*; **5**. *Yes, I drink alcohol 3 or 4 days per week*; **6**. *Yes, I drink alcohol 1 or 2 days per week*; **7**. *Yes, I drink alcohol 2 or 3 days per month*; **8**. *Yes, but only rarely* [310]. The respondents indicating that they were current drinkers were then asked 'On a day that you have an alcoholic drink, how many standard drinks do you usually have?'. At this stage a standard drink was defined to the respondent as 'a small glass of wine, a 285ml glass of regular beer, a nip of

spirits or a mixed drink' [310]; this equates to just over a UK unit of alcohol[3]. The respondents could then choose from one of the seven following answers: **1**. *13 or more standard drinks*; **2**. *11-12 standard drinks*; **3**. *9-10 standard drinks*; **4**. *7-8 standard drinks*; **5**. *5-6 standard drinks*; **6**. *3-4 standard drinks*; **7**. *1-2 standard drinks*.

This format of alcohol behaviour questions is termed 'quantity/frequency' measurement [308]. Weekly alcohol consumption is defined as the frequency of drinking days in a week multiplied by the quantity of drinks consumed on a usual drinking day. A point measure of weekly alcohol consumption is preferable to an interval, but the data collected in HILDA is interval data. Using the mid-point of interval values for quantity and frequency of drinking is standard practice in analyses of similar data [311-313] .

Estimated alcohol consumption for an individual in the sample in terms of usual number of drinks per week is therefore defined as follows:

$$consumption_i = [midpoint(usual\ quantity_i)\ ] * [midpoint(usual\ frequency_i)]$$

The binary variable '*at-risk drinker*' can therefore be generated, with the value of 1 if $consumption_i$ is greater than the threshold level for hazardous drinking, as defined separately for men and women.

It could be argued that dichotomisation of alcohol data at this stage is unnecessary: interval regression can be used to model equations where the dependent variable is in interval form, and no data on 'at-risk' status would be lost. Similarly, tobacco data is in 'count' form in the survey; regression techniques designed specifically for this type of data are available, such as the zero-inflated negative binomial model [314]. However, there is no software currently available to jointly estimate two such models and programming would be complex and time consuming. Treating tobacco and alcohol use data as binary choice data at this stage enables joint analysis of smoking and alcohol use, within the scope of this research project.

[3] One unit of Australia is defined as 10 grams of pure alcohol, as opposed to the definition of 10 ml of alcohol in the UK. One gram of water is equivalent to 1 gram of water, but the density of alcohol is different to that of water. Allowing for the density of alcohol, 1 Australian unit equates to 1.27 UK units.

The Self-Completion Questionnaire has contained questions on tobacco use since inception. In the first survey wave respondents were asked 'Do you smoke tobacco?', and in subsequent years this was altered slightly to 'Do you smoke cigarettes or any other tobacco products?' [310]. The potential responses to this altered question comprise: **1**. *No, I have never smoked*; **2**. *No, I no longer smoke*; **3**. *Yes, I smoke daily*; **4**. *Yes, I smoke at least weekly (but not daily)*; **5**. *Yes, I smoke less often than weekly* [310]. From these data it was possible to generate the binary variable '*smoker*', equal to 1 when an individual is a current smoker and equal to 0 for ex- or never-smokers.

One-wave lagged variables '*at-risk drinker last year*' and '*smoker last year*' were generated from these variables, in order to model state dependency, as discussed in Section 5.5. Table 4 describes the correlation between last year's drinking status and current drinking status. There is clear positive correlation; 34.95% of responses from those reporting at-risk drinking last year reported current smoking, compared to only 17.18% of responses from those not drinking to at-risk levels last year. Table 5 describes correlation between last year's smoking status and current drinking status; the strength of positive correlation is again clear. Chi-squared statistics were 1,950 and 2,076 respectively for Table 4 and Table 5 data, and clearly reject the null hypothesis of no expect differences between groups at a 1% significance level. Tetrachoric correlation coefficients, useful specifically for estimating correlation between binary variables and also reported in Table 4 and Table 5, further highlight the strength of correlation.

Table 4: Correlation between smoking status and last year's drinking status

		Current smoking status			
		Smoker		Non-smoker	
Last year's drinking status	At-risk	4,105	**34.95%**	7,641	**65.05%**
		27.80%		**12.94%**	
	Not at-risk	10,659	**17.18%**	51,400	**82.82%**
		72.20%		**87.06%**	

Tetrachoric rho = 0.3087

Test of null hypothesis last year's drinking status and current smoking status are independent: p = 0.000

Table 5: Correlation between drinking status and last year's smoking status

		Current drinking status			
		At-risk		Not at-risk	
Last year's smoking status	Smoker	4,268	**28.30%**	10,814	**71.70%**
		35.86%		**17.47%**	
	Non-smoker	7,634	**13.00%**	51,080	**87.00%**
		64.14%		**82.53%**	

Tetrachoric rho = 0.3160

Test of null hypothesis last year's smoking status and current drinking status are independent: p = 0.000

Theory and simple data analysis (cross-tabulation, Chi-squared tests) of correlation between covariates and dependent variables were used to aid decision making about appropriate sub-division of covariates for the regression analysis. Model fit with different covariate specification was also considered where appropriate, using Akaike information criterion (AIC) and Bayesian information criterion (BIC) post-estimation [315].

Four previous analyses found evidence that the level of education achieved by an individual to be a significant factor in determining alcohol and tobacco behaviours [270, 275, 278, 316]. In these studies, higher education was associated with better health behaviours in terms of tobacco [270, 275, 278, 316], but worse health behaviours in terms of alcohol [270, 275, 316]. The dichotomous variables '*none or secondary education*', '*vocational*' and '*graduate*' were generated from information on the highest level of education attained by HILDA respondents. The variable '*none or secondary education*' signals that an individual achieved no qualifications beyond basic secondary educations; '*vocational*' implies further, non-academic qualifications have been achieved; '*graduate*' signals completion of an undergraduate university degree. Responses from the categories '*vocational*' and '*graduate*' showed significantly higher proportions of excessive drinking and smoking participation, respectively. There were no significant differences in

smoking and excessive alcohol use status within '*none or secondary education'* and this was used as the reference category.

Several of the previous analyses identified in the review found marital status to be a significant determinant of alcohol and tobacco behaviour [270, 275, 278, 316]. Marriage has been shown to be negatively associated with smoking [270, 275, 278, 316], and evidence points to a weaker negative association with alcohol use [270, 275]. From the data it was possible to identify separate groups for those that are (i) Married; (ii) Widowed; (iii) Divorced; (iv) Separated but not divorced; (v) Never married but living with a partner; (vi) Never married and not living with a partner. The corresponding dichotomous variables '*married'*, '*widowed'*, '*divorced'*, '*separated'*, '*never married but living with someone'* and *'never married and not living with someone'* were generated. The variable '*married'* was used as the reference category.

Age has been identified as a significant determinant of smoking behaviour and drinking behaviour in several of the key studies in the area [270, 275, 276, 278, 316]. The age, in years, of a respondent on the 30th of June in the wave year is collected routinely in HILDA (e.g. 2002 for wave 2). The variable '*age*' was created from these data.

Clarke and Etilé showed that health shocks made smokers more likely to smoke less and quit in future years, using BHPS data [317]. HILDA has collected information on whether respondents have long-term difficulty breathing or shortness of breath every year since the third wave of data, but very few in the sample have reported such problems. More general self-reported health measures have also been included in each wave through the General Health Questionnaire.

From these data it was possible to generate binary variables describing own health as 'good but not very good', 'fair', 'poor', 'very good' or 'excellent', and to generate binary variables characterising positive or negative changes over the past year. A binary variable signalling long-term chest or breathing problems was also created.

Prevalence of self-reported chest problems in the overall sample was low (< 3%), and tests supported the use of '*fair health*' and '*poor health*' as covariates with those reporting excellent, very good or good health as the reference category.

None of the studies reviewed in section 5.2 controlled for the effect of having children upon health behaviour. However, intuition and evidence suggest that having children may reduce the propensity to smoke and drink excessively. Analysis of a random sample of nearly 8,000 Canadian drinkers revealed that parenthood is associated with reduced heavy drinking for both mothers and fathers [318], while a prospective Dutch study found acquisition of a parental role was associated with a decrease in heavy drinking and general reduction in consumption [319]. Elsewhere, analysis of individual-level survey data from Great Britain and America found that having a daughter leads individuals to reduce their smoking and drinking, relative to having a son [320]. The HILDA sample supports these findings, though the negative correlation between child presence and propensity to smoke in the sample is greater.

The binary variable '*child resident*' was used as a covariate in the analysis, with a value of 1 if a respondent had their own or adopted child currently residing in the parental home, and 0 otherwise.

Price indices for tobacco and alcohol have been used widely in the econometrics literature to estimate interdependencies between drinking and smoking habits [275, 277, 289, 290, 292, 293, 316]. It has been seen though that results have differed across studies. The appeal of using 'cross-price elasticity' as a measurement tool is based on the assumed exogeneity of price indices as regressors. As discussed in the review above though, the impact of price changes in one good upon use of another good only tells part of the story. Including price indices for tobacco and alcohol as covariates may enable some understanding of whether propensity to smoke or partake in 'risky' alcohol consumption is influenced by changes in real alcohol and tobacco prices, and avoid potential 'omitted variable bias' problems.

In order to control for changes in the real price of tobacco and alcohol products, Australian Consumer Price Index (CPI) data from the Australian Bureau of Statistics (ABS) [321] was appended to the HILDA dataset. The ABS holds quarterly index number data on groups and sub-groups of consumer goods. 'Tobacco' and 'Alcoholic Drinks' are two of nearly 150 categories of consumables recorded [321].

The ABS data documents separate CPI information for each of eight cities in Australia: Sydney, Melbourne, Brisbane, Adelaide, Perth, Hobart, Darwin and Canberra [321]. The HILDA dataset allows identification of the place of residence of each respondent by eight regions, and each of these regions includes one of the major cities listed above. These eight regions and their corresponding cities are as follows: New South Wales (Sydney); Victoria (Melbourne); Queensland (Brisbane); South Australia (Adelaide); Western Australia (Perth); Tasmania (Hobart); Northern Territories (Darwin); Australian Capital Territory (Canberra) [310].

By using the city CPI data from ABS as a proxy for regional price data, it was possible to attribute CPI figures for tobacco and alcohol to individuals in the HILDA dataset, according to their region of residence. While ABS CPI data are collected quarterly, in March, June, September and December, HILDA respondents contribute to the dataset annually [321, 322]. It was important to select the CPI figures that most closely matched the time of HILDA data collection. However, data collection for HILDA takes place over a number of months each year. Helpfully, documentation of the percentage of interviews collected in each month is published in annual reports available from the HILDA website[4].

Using these figures, it was possible to weight the CPI value attributed to individuals in the HILDA dataset according to the proportion of interviews collected at different time points. The variables '*price index alcohol*' and '*price index tobacco*' are therefore wave- and region-specific price index variables with values for all respondents in the dataset, and included as scaled-down covariates in regression analyses.

There was some suggestion from previous studies in this area that income is a determinant of tobacco and alcohol behaviours, over time [289] and across individuals [270, 275]. HILDA contains detailed personal and household income information. The aim of including an income measure as a covariate is to further capture the impact of spending power upon propensity to participate in harmful health behaviours; household, rather than personal, income is reasoned to better represent this power. A measure of household annual disposable income best

[4] http://www.melbourneinstitute.com/downloads/hilda/Annual_Report/areport2011.pdf (last accessed April 2014)

captures spending power. To transform these data into real terms, ABS price index data was again used.

The variable '*real household annual disposable income'* merited one further transformation. The relationship between disposable income and propensity to drink alcohol and smoke is non-linear, increasing with low levels of income before tailing off and decreasing with higher income levels. The natural log transformation in equation (16) was performed, whereby 1 was added to avoid computing the natural log of zero:

$$lnrealHHanndispinc = \ln((real\ household\ annual\ disposable\ income) + 1) \quad (16)$$

The variable '*natural logarithm of real household annual disposable income*' was included as a covariate in regression analysis.

Exploratory data analysis unveiled positive correlation between unhealthy behaviours and major city residence. A dummy variable 'Major City', with value 1 if the respondent resides in Sydney, Melbourne, Brisbane, Adelaide or Perth, and 0 otherwise, was included as a covariate in regression analysis.

Though not encountered in the review of the econometrics literature, the panel nature of the HILDA data allows estimation of the impact of key temporal events upon the variables of interest.

Initially, it was of interest to analyse how tobacco participation and alcohol participation have changed over time. Cross tabulation of the wave of data with the variables '*smoker'* and '*at-risk drinker'*, respectively, showed that smoking prevalence has decreased over the period 2002 to 2009, whereas hazardous drinking prevalence has remained almost constant.

There has been no change in excessive alcohol use prevalence between 2002 and 2009 among respondents, though this simple analysis could mask changes in the distribution of at-risk drinking. There is however clear variation in smoking prevalence over time. This could be viewed as a continuing response to policies from regional and central Australian Governments aimed at reducing smoking behaviour in the population. The only key policy change over this period has been

the introduction of total enclosed area smoking bans on licensed premises (similar to the July 2007 smoking ban in the UK) [323]. The dichotomous variable '*smoking ban*' was generated, with a value of 1 if total bans on smoking in enclosed public areas were in place and a value of 0 otherwise. Such bans were in place in all states and territories by the end of 2007, bar the Northern Territory, but came in to force at different times across Australia. This is reflected in the variable '*smoking ban*'.

5.5. Econometric Framework

Following the theoretical discussion of section 5.3, and existing psychological, clinical and economic literature, the decisions to participate in two addictive and unhealthy behaviours are assumed to be jointly determined. Section 5.5 sets out the econometric framework to estimate joint participation decisions for smoking and excessive drinking. Specific issues addressed include treatment of state dependence and unobserved individual heterogeneity, the initial conditions problem in dynamic processes, and parameter estimation.

The decisions to smoke and participate in excessive drinking are modelled as dynamic interdependent processes, and the model used is a dynamic bivariate probit with unobserved individual heterogeneity. A bivariate extension of the dynamic probit model was proposed by Alessie *et al* in 2004 in order to analyse the dynamics of ownership of stocks and mutual funds [324]. A similar specification has been employed in several analyses since: to investigate social exclusion and poverty [325]; to analyse links between spouses in obesity [326] and separately spousal links in the decision to smoke [327]; to consider as joint processes migration and high school graduation in Mexico [328]; and to jointly model decisions to leave home and to enter employment in Britain [329]. One application of a dynamic bivariate probit model has used HILDA data. Lee and Oguzoglu jointly modelled positive well being and negative well being ('ill-being') using the first five waves of HILDA [330].

Two key econometric issues the dynamic bivariate probit model tackles were first addressed in the context of a univariate dynamic probit. As early as 1981, Heckman proposed an econometric framework that dealt with the linked problems of unobserved individual heterogeneity and state dependence in econometric applications [331, 332].

In many situations, experiencing an event in the past increases the probability of experiencing that event in the future [332, 333]. This can apply to various different contexts, such as the probability of a leg break for a footballer, and is particularly relevant for the study of addictive behaviours. It is well established that past alcohol and cigarette use are predictive of future use [267].

This phenomenon was described by Heckman as 'state dependence' [331, 332]. Heckman was keen to highlight two different forms of state dependence: *false* and *true* [332]. If experiencing an event in the past changes preferences or probabilities relevant to present choices or outcomes, so that behaviour or outcomes now are different to an identical individual that did not experience the event, there is *true* state dependence [332]. At the same time, unobserved differences between individuals could drive preferences or probabilities relevant to choices or outcomes. If this unobserved individual heterogeneity is linked to past experience of the event, past experience could act as a proxy for these unobserved differences, and give a false impression that past experience is important [333]. This is *false* state dependence.

To expand with reference to examples, our footballer's probability of leg break could be increased by a past break as the bone structure is permanently damaged (true state dependence), or this could appear to be the case when an unobserved genetic calcium deficiency means elevated risk of a leg break at any point in time (false state dependence). For addictive behaviour outcomes, past cigarette smoking could be predictive of current cigarette smoking because smoking in the past has increased the utility derived from cigarettes (true state dependence), or because inherent taste for rebellious behaviour makes an individual more likely to smoke at any time (false state dependence).

Heckman's proposed model dealt with the problem of distinguishing between true and false state dependence [332]. The following model is a simple extension of the univariate dynamic probit in that a second equation is added and cross-dynamics are introduced [329]:

$$y_{1it}^{*} = \delta_{11} y_{1it-1} + \delta_{12} y_{2it-1} + \beta_1 X_{1it} + v_{1i} + u_{1it} \quad (17)$$

$$y^*_{2it} = \delta_{21} y_{1it-1} + \delta_{22} y_{2it-1} + \beta_2 X_{2it} + v_{2i} + u_{2it} \quad (18)$$

$$y_{jit} = 1 \; if \; y^*_{jit} > 0 \; and \; 0 \; otherwise, \qquad j = 1,2; i = 1,..,N; t = 1,...,T$$

To apply this model to the work at hand, $y_1$can be considered a binary variable signalling smoking participation, y_2 a binary variable signalling at-risk alcohol use. X_{jit} are exogenous observable explanatory variables, v_{ji} are time-invariant unobservable characteristics and u_{jit} are random errors. It is clear that equations (17) and (18) are similar to equations (14) and (15), with the key difference the problem is now one of discrete choices.

The unobserved error elements of (17) and (18) can be described by the following random effects structure :

$$\varepsilon_{jit} = v_{ji} + u_{jit} \quad (19)$$

The time-invariant 'random' effects $v_{1i}$and v_{2i} are assumed to follow a bivariate normal distribution with variances σ^2_{v1} and σ^2_{v2} and correlation ρ_v, while u_{1it} and u_{2it} are independent over time but also follow a bivariate normal distribution, with unit variances and correlation ρ_u [325, 334]. With these assumptions, the ε_{jit}, conditional on the observed X_{jit}, are bivariate normal with mean zero and the following covariance matrix [326, 329]:

$$\begin{bmatrix}\varepsilon_{1it}\\ \varepsilon_{2it}\end{bmatrix} = N\sim\left(0, \; \begin{bmatrix} 1+\sigma^2_{v1} & \sigma_{v1}\sigma_{v2}\rho_v + \rho_u \\ \sigma_{v1}\sigma_{v2}\rho_v + \rho_u & 1+\sigma^2_{v2}\end{bmatrix}\right) \quad (20)$$

$$Cov(\varepsilon_{jit}\varepsilon_{jis}) = \sigma^2_{vj}/(1+\sigma^2_{vj}), \; t \neq s.$$

As the model explicitly accounts for unobserved individual heterogeneity, it is well equipped to capture *true* state dependence. The coefficients δ_{11} and δ_{22} in equations (17) and (18) inform whether 'own'-state dependence is important; that is, if smoking in the previous time period actually affects the probability of smoking in the current time period.

Similarly, the model enables understanding of whether correlation between y_{1it} and y_{2it-1} (or y_{2it} and y_{1it-1}) is due to true 'cross'-state dependence ($\delta_{12}, \delta_{21} \neq 0$) or correlation between unobserved heterogeneity ($\rho_v \neq 0$) [325]. This distinction is of primary interest. If there is a significant causal positive effect of previous smoking upon the probability of participating in excessive alcohol use, then the overriding narrative of strategies to tackle alcohol misuse is blind to an important factor. This analysis of course also has the potential to inform on whether decision makers should explicitly consider excessive alcohol use in the development and implementation of anti-tobacco strategies.

It is worth noting that the model described reduces to the univariate case in some situations. If $\delta_{12} = \delta_{21} = 0$, parameters in equations (17) and (18) can be estimated separately as two dynamic probit models with only a potential loss of efficiency [325]. If $\delta_{12} \neq 0$ but there is zero cross-equation correlation between unobserved individual effects and between errors ($\rho_v = \rho_u = 0$), equation (17) can be estimated as a univariate model where y_{1it-1} is weakly exogenous [325]. Similar logic applies to equation (16). For all other cases, joint estimation is demanded.

So far, a problem encountered in dynamic models with unobserved time-invariant heterogeneity and limited time periods has been ignored. In equations (17) and (18) the presence of v_{1i} and v_{2i} renders own-state dependence variables y_{1it-1} and y_{2it-1} endogenous, as seen in the case of Picone *et al* in Section 5.2 [267] and illustrated by implied equations (21) and (22) below:

$$y^*_{1it-1} = \delta_{11} y_{1it-2} + \delta_{12} y_{2it-2} + \beta_1 X_{1it-1} + v_{1i} + u_{1it-1} \tag{21}$$

$$y^*_{2it-1} = \delta_{21} y_{1it-2} + \delta_{22} y_{2it-2} + \beta_2 X_{2it-1} + v_{2i} + u_{2it-1} \tag{22}$$

Clearly, lagged dependent variables y_{1it-1} and y_{2it-1} are endogenous in equations (17) and (18) as they depend upon v_{1i} and v_{2i}, respectively. For consistent estimation, modelling y^*_{jit-1} for all $(t = 1, \dots, T)$ would be sufficient, but impossible

for $t = 1$ given there is no previous data panel [335]. Cross-state dependence variables are also endogenous in (17) and (18), as they are correlated with the u_{jit} when $\rho_u \neq 0$ [335].

A simple solution would be to assume that pre-sample data is exogenous and can be ignored [332]. In the present case, this would mean imposing serial independence upon the disturbances generating the dynamic process (untrue in the presence of time-invariant unobserved heterogeneity) or assuming the smoking participation decision each HILDA respondent made in their first wave of data collection was truly their first smoking participation decision (highly unlikely).

Another solution to these problems is to initialise the dynamic process that is being generated [331]. With reference to the univariate case, Wooldridge built on an approach proposed by Heckman to suggest modelling unobserved individual heterogeneity as a function of the endogenous initial value [336]. This approach is easily extended to the bivariate case, where the individual-specific unobserved effects v_{1i} and v_{2i} are each modelled as functions of both initial values y_{1i1} and y_{2i1} and time-averaged covariates $\bar{X}_{ji}$ as follows:

$$v_{1i} = \zeta_{11} + \zeta_{12} y_{1i1} + \zeta_{13} y_{2i1} + \zeta_{14} \bar{X}_{1i} + \alpha_{1i} \tag{23}$$

$$v_{2i} = \zeta_{21} + \zeta_{22} y_{1i1} + \zeta_{23} y_{2i1} + \zeta_{24} \bar{X}_{2i} + \alpha_{2i} \tag{24}$$

In equations (23) and (24), the ζ_{jk} $(k = 1, \dots, K)$ are parameters to be estimated and α_{ji} are normally distributed with the following covariance matrix [325]:

$$cov(\alpha_{1i,}\alpha_{2i}) = \begin{bmatrix} \sigma_{\alpha 1}^2 & \sigma_{\alpha 1}\sigma_{\alpha 2}\rho_\alpha \\ \sigma_{\alpha 1}\sigma_{\alpha 2}\rho_\alpha & \sigma_{\alpha 2}^2 \end{bmatrix} \tag{25}$$

Substituting equations (23) and (24) into equations (17) and (18) leads to the model as follows:

$$y^*_{1it} = \delta_{11} y_{1it-1} + \delta_{12} y_{2it-1} + \beta_1 X_{1it} + \zeta_{11} + \zeta_{12} y_{1i1} + \zeta_{13} y_{2i1} + \zeta_{14} \bar{X}_{1i} + \alpha_{1i} + u_{1it} \quad (26)$$

$$y^*_{2it} = \delta_{21} y_{1it-1} + \delta_{22} y_{2it-1} + \beta_2 X_{2it} + \zeta_{21} + \zeta_{22} y_{1i1} + \zeta_{23} y_{2i1} + \zeta_{24} \bar{X}_{2i} + \alpha_{2i} + u_{2it} \quad (27)$$

The underlying propensity to smoke (drink to at-risk levels) is explained by last year's smoking and drinking status, contemporaneous independent variables detailed in Section 5.4 and initial smoking (drinking), which is assumed to be a function of initial observed behaviour and time-averages of the contemporaneous independent variables. Consistent parameter estimates for equations (26) and (27) can be obtained using the estimation procedure described below.

This adaptation of Wooldridge's solution to the 'initial conditions' problem has been implemented by several of the existing dynamic bivariate probit model studies [325, 327, 329, 335]. Others have used an adaptation of Heckman's original approach [324, 330, 334, 337]. With reference to the univariate case, Heckman proposed specifying an auxiliary equation for the process that generated the initial observed values, then estimating the model allowing correlation between the initial and main equations [329, 331]. Because this amounts to modelling the initial value as a function of unobserved individual heterogeneity, it has been described as the opposite to Wooldridge's method [329]. Alessie *et al* were the first to extend this model to the bivariate case [329]. As with the Wooldridge approach, this extension is straightforward.

Because in practice the Heckman approach would mean four integrals in comparison to Wooldridge's two, the Wooldridge approach is less computationally expensive [325, 329]. This is the primary reason for using Wooldridge's solution here: reducing estimation time is a practical priority. In addition though, while one group has raised concern over bias in adapted versions of Wooldridge's solutions when few waves of data have been used [338], research has suggested that the Wooldridge approach performs at least as well as a Heckman-style approach for panel data with five or more waves [339].

Wooldridge argues that for random effects estimation of panel data models, time period dummy variables should be included as control variables if they are statistically significant: omitting them could cause serial correlation in the idiosyncratic error term [340]. Dummy variables for each wave were included in static bivariate random effects models, but none were significant at the 10% level and were subsequently excluded from final estimation equations.

5.5.1. The sample and survey non-response and attrition

Estimation of this dynamic bivariate model requires a 'compact panel' [329]. That is, observations from each individual must be consecutive and contain no gaps in time[5]. The obvious approach, and that used in many previous studies [325, 327, 330], is to use the balanced panel. This means dropping all observations from individuals with gaps, however: a significant loss of useful data. In order to use all possible data, a sensible and appropriate alternative is to keep the longest consecutive spell of observations from each individual. This would mean that as well as all observations from an individual with full responses to all variables in each wave being used, observations from an individual who joined the sample in wave 4 and subsequently responded fully in each wave would be used. The 'longest spell' panel contained 44,646 observations from 9,309 men and women for estimation; the balanced panel contained 28,665 observations from 4,095 men and women. Using the balanced, instead of the 'longest spell' panel, is to discard 35% of observations and 56% of individuals from the 'longest spell' sample. For completeness, the analysis was run for both the balanced panel and the 'longest spell' unbalanced panel. Descriptive statistics for key variables in estimation samples are reported in Table 44 of Appendix D.

Using survey panel data to model health-related behaviour creates a potential problem of bias from non-response or attrition. Sampling for the first wave of the HILDA survey was designed so that the sample reflected the population of households occupying private dwellings in Australia; this sample then formed the basis for the panel of households to be followed over subsequent waves [341]. New entrants to panel households are added to the sample as temporary or permanent

[5] The estimation code works by estimating the log-likelihood function for each individual and then summing across individuals. The code cannot identify missing observations within an individual, however: if an individual leaves the sample and then returns, the code is unable to detect this.

(births or parents of sample births) sample members, and panel members leave the sample either temporarily, perhaps due to ill health, or permanently, because they either migrate overseas or die [341]. In this application, if the reason for leaving the sample is linked to smoking participation, or at-risk alcohol behaviour, then systematic attrition is a threat to the consistency of covariate parameter estimates. Death and ill health can be caused by smoking and at-risk alcohol use, and so potential attrition bias deserves attention.

Continuing panel members may also non-respond to certain or all questions in the survey, for some or all years. Again, if this non-response is related to the dependent variables, bias is a concern. It is easy to imagine such a scenario: a respondent might contract a temporary but debilitating respiratory illness caused by smoking meaning they cannot respond for one wave; another respondent might become embarrassed by their excessive alcohol consumption, and so avoid answering specific questions about alcohol use. In this way, it can be seen that the problem of non-response can be similar to that of under-reporting in self-report surveys.

It is important to test for the presence of attrition bias in this study. However, the consequence of attrition bias for cross-state dependence parameter estimates (δ_{12} and δ_{21} in equations (26) and (27), respectively) is of primary interest. Over-estimation of cross-state dependence could lead to over-estimation of knock-on health benefits of improving smoking (drinking) behaviour. This would create bias in favour of more costly and more effective behaviour-change strategies in economic evaluation under the proposed framework. The consequence of this is potentially favouring a 'wrong' adoption decision.

Jones *et al* have highlighted measures to test for attrition bias in regression models [342], first proposed by Verbeek and Nijman [343]. These measures are essentially 'variable addition tests': variables describing the pattern of survey response are generated and included as covariates in the regression equations of interest run on the full unbalanced sample [342]. Three variables describing survey response are suggested [342, 343]. '*Ti*' is a count variable reflecting the number of survey waves individual 'i' is in the sample. The dummy variable '*all waves*' describes presence in

the balanced panel. In this application the balanced panel comprises seven waves[6]. Lastly, '*next wave*' is a dummy variable indicating presence in the sample in the following wave. Tests of the statistical significance of these survey response variables provide tests for attrition bias [342].

These tests were designed to run on the full unbalanced sample, and as such are not suited to the dynamic bivariate random effects probit model: the samples available for final model estimation are (i) the balanced panel and (ii) the 'longest spell' unbalanced panel, as discussed above. However, relaxing assumptions imposed upon individual errors and estimating equations (26) and (27) separately as (i) pooled static probit models and (ii) dynamic random effects probit models using the full unbalanced panel, performing the attrition tests described, gave indication of the presence of non-response bias in this study.

Where non-response bias was indicated to be present from these tests, the potential influence of non-response bias for cross-state dependence estimates was investigated in reduced specifications of the model. Jones *et al* prescribe correcting for attrition bias using 'inverse probability weights'[342]; essentially, this involves favourably weighting observations from individuals with higher probability of non-response. This method does not easily lend itself to the full model specification here though, and has limitations. To generate 'inverse probability weights', equations for response versus non-response at each wave after the first wave are estimated, conditional on a set of observable characteristics, s_{i0}, not used elsewhere in the model, that are measured at the first wave [342]. This relies on non-response being ignorable, conditional on s_{i0} [342, 344], and so breaks down if non-response is caused by unobserved health shocks that are systematically linked to the outcome. Practicality is also a consideration. An appeal of the Jones *et al* method in health econometric applications is that it is easy to apply to binary outcome models: estimates for a weighted probit model can be generated by maximum likelihood using the 'pweight' sub-command in recent versions of Stata [342, 345]. Interpretation of results from these reduced-specification models was the limit of investigation into attrition bias in this chapter.

[6] There are nine waves of data available (waves 2 to 10 of HILDA), but the first two waves are used to model initial conditions and lagged explanatory variables.

5.5.2. Estimation

The parameters of the model described were estimated by MSL. Before setting out the likelihood function and describing the MSL process, it is first useful to define the probabilistic statements that contribute to the likelihood function [335].

Equations (28) and (29) define two $[1\ x\ K]$ vectors containing the variables on the right hand side of equations (26) and (27), while equations (30) and (31) below defines two $[K\ x\ 1]$ vectors containing the corresponding parameters, where intercept terms ζ_{j1} are included in β_j [326]:

$$\pi_{1it} = [y_{1it-1}\ y_{2it-1}\ X_{1it}\ \ y_{1i1}\ y_{2i1}\ \bar{X}_i] \tag{28}$$

$$\pi_{2it} = [y_{1it-1}\ y_{2it-1}\ X_{2it}\ \ y_{1i1}\ y_{2i1}\ \bar{X}_i] \tag{29}$$

$$\eta_1 = [\delta_{11}\ \delta_{12}\ \beta_1\ \zeta_{12}\ \zeta_{13}\ \zeta_{14}\ ]' \tag{30}$$

$$\eta_2 = [\delta_{21}\ \delta_{22}\ \beta_2\ \zeta_{22}\ \zeta_{23}\ \zeta_{24}\ ]' \tag{31}$$

The following conditional probabilistic statements can now be made, where $\Phi[.,.;.]$ is the cumulative distribution function of the bivariate standard normal distribution [335]:

$$\Pr(y_{1it} = 1, y_{2it} = 1|\pi_{1it}, \pi_{2it}, \alpha_{1i}, \alpha_{2i}) = \Phi\ [(\pi_{1it}\eta_1 + \alpha_{1i}), (\pi_{2it}\eta_2 + \alpha_{2i}); \rho_u] \tag{32}$$

$$\Pr(y_{1it} = 1, y_{2it} = 0|\pi_{1it}, \pi_{2it}, \alpha_{1i}, \alpha_{2i}) = \Phi\ [(\pi_{1it}\eta_1 + \alpha_{1i}), -(\pi_{2it}\eta_2 + \alpha_{2i}); -\rho_u] \tag{33}$$

$$\Pr(y_{1it} = 0, y_{2it} = 1|\pi_{1it}, \pi_{2it}, \alpha_{1i}, \alpha_{2i}) = \Phi\ [-(\pi_{1it}\eta_1 + \alpha_{1i}), (\pi_{2it}\eta_2 + \alpha_{2i}); -\rho_u] \tag{34}$$

$$\Pr(y_{1it} = 0, y_{2it} = 0|\pi_{1it}, \pi_{2it}, \alpha_{1i}, \alpha_{2i}) = \Phi\ [-(\pi_{1it}\eta_1 + \alpha_{1i}), -(\pi_{2it}\eta_2 + \alpha_{2i}); \rho_u] \tag{35}$$

With probabilistic statements for all possible outcomes of the joint decisions over whether to smoke and whether to excessively drink captured by equations (32), (33), (34) and (35), the probability that a discrete random variable is exactly equal to a value can be expressed as follows [335]:

$$f(y_{1it}, y_{2it}|\pi_{1it}, \pi_{2it}, \alpha_{1i}, \alpha_{2i}) = \Phi\,[q_{1it}(\pi_{1it}\eta_1 + \alpha_{1i}), q_{2it}(\pi_{2it}\eta_2 + \alpha_{2i}); q_{1it}q_{2it}\rho_u] \quad (36)$$

$$q_{jit} = 2y_{jit} - 1\,, \qquad j = 1{,}2$$

Outcomes are assumed to be conditionally independent over time, and so their joint density for an individual can be written [329, 335]:

$$\prod_{t=1}^{T} f(y_{1it}, y_{2it}|\pi_{1it}, \pi_{2it}, \alpha_{1i}, \alpha_{2i}) = \prod_{t=1}^{T} \Phi\,[q_{1it}(\pi_{1it}\eta_1 + \alpha_{1i}), q_{2it}(\pi_{2it}\eta_2 + \alpha_{2i}); q_{1it}q_{2it}\rho_u] \quad (37)$$

It is now possible to state the likelihood function for the ith individual in equation (38), defining the parameters to be estimated as $\theta = [\,\eta_1\ \eta_2\ \sigma_{\alpha 1}^2\ \sigma_{\alpha 2}^2\ \rho_\alpha\ \rho_\varepsilon\,]$`, given the distributional assumption imposed on α_{1i} and α_{2i}:

$$l_i(\theta) = \int_{\alpha_1}\int_{\alpha_2} \prod_{t=1}^{T} \Phi\,[q_{1it}(\pi_{1it}\eta_1 + \alpha_{1i}), q_{2it}(\pi_{2it}\eta_2 + \alpha_{2i}); q_{1it}q_{2it}\rho_u]\, h(\,\alpha_1, \alpha_2)\, d\alpha_1 d\alpha_2 \quad (38)$$

The log-likelihood function for the entire sample can therefore be written as:

$$logL(\theta) = \sum_{i=1}^{N} log\, l_i(\theta) \quad (39)$$

It now remains to calculate parameters θ, but the individual likelihood in equation (38) contains double integrals. It is possible to estimate by ML using quadrature or MSL, which essentially approximates the individual likelihood, instead of solving analytically.

The MSL procedure adopted works by randomly drawing R values from the bivariate normal distribution of the unobserved individual effects $\alpha_1$and α_2,

$\{(\alpha_{1i}^1, \alpha_{2i}^1), .., (\alpha_{1i}^r, \alpha_{2i}^r)\}$, so that for given values of η_1 and η_2, the individual likelihood in (38) is approximated by equation (40) [325, 329, 335]:

$$\widetilde{l_i}(\theta) = \frac{1}{R}\sum_{\alpha_{1i}^r, r=1}^{R}\sum_{\alpha_{2i}^r, r=1}^{R}\{\prod_{t=1}^{T}\Phi\,[q_{1it}(\pi_{1it}\eta_1 + \alpha_{1i}^r), q_{2it}(\pi_{2it}\eta_2 + \alpha_{2i}^r); q_{1it}q_{2it}\rho_u]\} \quad (40)$$

Halton draws are well spaced non-random draws contained within the unit interval and have been shown to have better coverage than simple pseudo-random draws in various discrete choice model simulations [346, 347]. Halton draws were therefore used in place of more simple pseudo-random draws in this application. The appropriate number of draws was tested by analysing changes in log likelihood as the number of draws was increased. Halton sequence generation and simulated likelihood maximisation were performed in Stata, version 11 [345], using code written for an earlier application of the bivariate dynamic random effects model noted here [325], and made available by the author, Professor Francesco Devicienti.

5.6. Results

This subsection reports and interprets results from the dynamic bivariate random effects probit model described above. For the purpose of comparison, results from univariate dynamic models, a 'restricted' version of the dynamic bivariate model where $\rho_v = \rho_u = 0$, are also reported in Appendix D. Problems encountered with estimation are described first, before the results are interpreted. Results of investigations into potential attrition bias in the estimates are also presented.

5.6.1. Estimation Results

It was necessary to use a compact panel sample, as discussed above, and the intention was to estimate the model by gender separately for (i) the 'longest spell' sample, making maximum use of the data and (ii) the balanced panel, as seen elsewhere [336]. However, the complexity of the model meant that the results would not converge when balanced samples were used: the estimation procedure encountered a flat or discontinuous region in the log-likelihood function. Numerous attempts were made to validly overcome this hurdle. First, within-variation in covariates was examined, to rule out the possibility of zero or very small variation in one or more covariates. This proved, unsurprisingly, to be the case for education variables. Time-averages of these variables were removed from

the initial conditions equations (23) and (24) in an effort to aid estimation. Second, different starting values for the estimation process were used. The default starting point used parameter estimates from the static bivariate random effects probit model; estimates from dynamic univariate models and the dynamic bivariate model using the 'longest spell' sample were also tried. Third, altering the order of the search algorithms was tried. The default optimisation code started with Stata's modified Newton-Raphson algorithm, switching to the Davidon-Fletcher-Powell algorithm and then the Broyden-Fletcher-Goldfarb-Shanno algorithm. None of these attempted solutions led the model to converge.

There were also problems estimating the model for women using the 'longest spell' sample. Again, the estimation procedure broke down upon encountering a flat or discontinuous region in the log-likelihood function. The steps described above to achieve model convergence were again attempted but were again unsuccessful. Results for women were generated, using the full 'longest spell' sample from men and women, with *male* included as an additional covariate.

Figure 8 and Figure 9 show changes in the log likelihood of parameter estimates as the number of Halton draws used to generate results was increased incrementally from 50 to 300. It would have been preferable to test results using higher numbers of Halton draws, but this was not possible given capacity limitations of the available software. The bivariate dynamic results presented here were generated using 300 Halton draws of unobserved individual effects.

Figure 8: Change in log-likelihood as number of Halton draws increased, male estimation sample

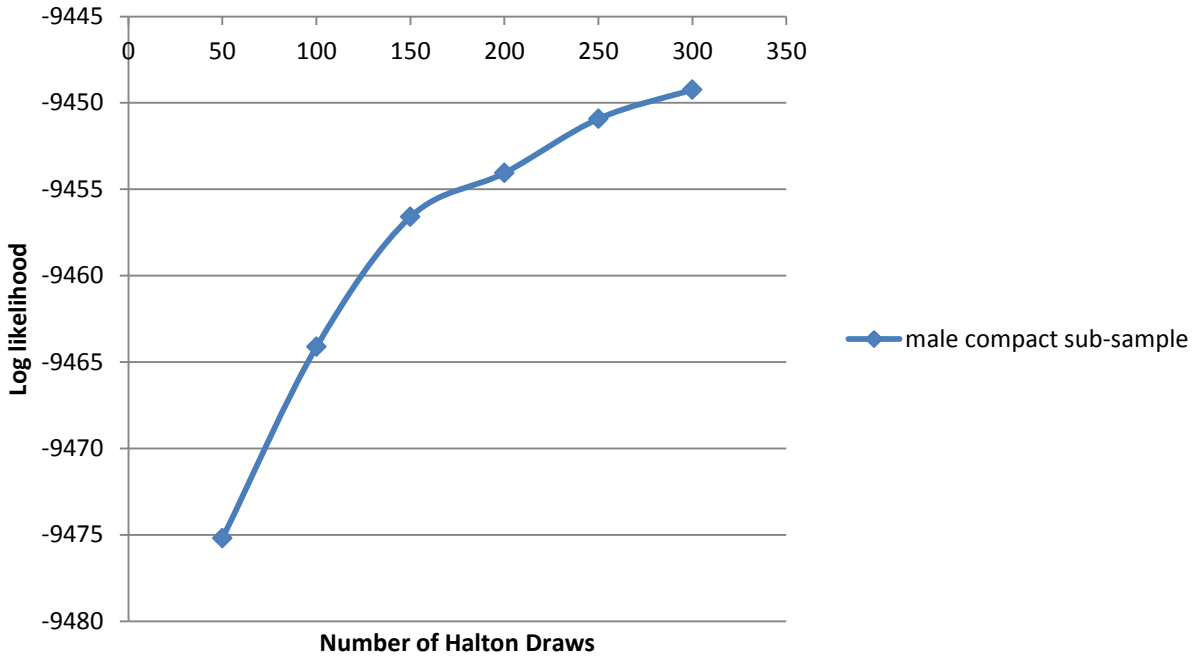
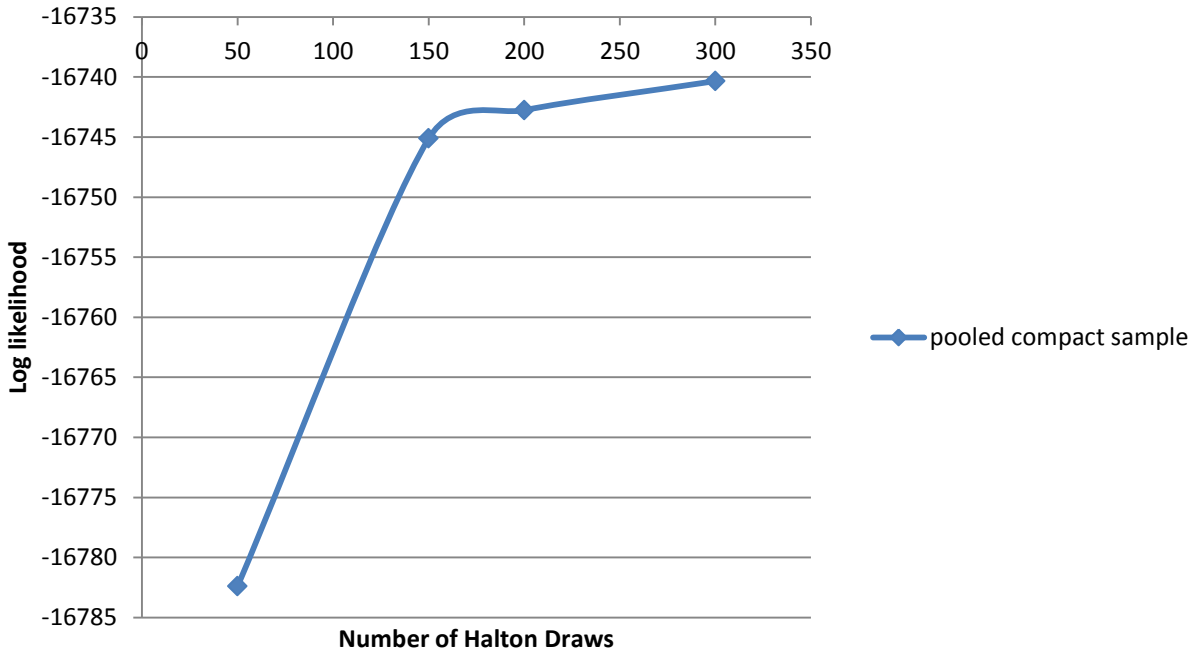


Figure 9: Change in log-likelihood as number of Halton draws increased, pooled estimation sample



Results from estimation of bivariate dynamic models are shown in Table 6; univariate dynamic model results are shown in Table 42 of Appendix D, for comparison. The bivariate model is justified on grounds of consistency, as there is evidence of both cross state dependency and correlation between unobserved individual heterogeneity, described in more detail below.

Columns (1) and (2) of Table 6 contain estimates for the male sub-sample; columns (3) and (4) contain estimates of results for the pooled sample containing both men and women. It can be seen that while the direction of parameter estimates are seldom different across the different samples, the influence of explanatory variables upon smoking and drinking outcomes is different for men and women. For example, own-state dependence is a stronger determinant of smoking status for women than men. The isolated gender effects in columns (3) and (4) suggest being male is an independent predictor of smoking and at-risk drinking.

True own-state dependence was found for both probability of smoking and probability of at-risk drinking, significant at the 1% level across samples. Controlling for observed and unobserved person-specific attributes, smoking in the previous time period makes an individual significantly more likely be a current smoker; at-risk drinking in the previous time period increases the probability of current at-risk alcohol use. This reaffirms results from Picone *et al* [267], and is the expected result given the wealth of literature on the addictiveness of alcohol and tobacco encountered in Chapter 2. This also highlights the limitations of the numerous analyses which have relied on cross-sections of data for inference about links between alcohol and tobacco use, and have therefore not been able to account for addiction in their analyses, clearly a key determinant of smoking and drinking behaviour.

Table 6: Dynamic Bivariate Probit Model Results

Variables	Men		Pooled	
	(1) Smoker	(2) At-risk Alcohol Use	(3) Smoker	(4) At-risk Alcohol Use
Smoker last year	1.527***	0.209**	1.641***	0.182***
	(0.000)	(0.016)	(0.000)	(0.007)
At-risk Drinker last year	0.060	0.850***	0.027	0.832***
	(0.456)	(0.000)	(0.652)	(0.000)
Smoker initial value	2.558***	0.164*	2.425***	0.224***
	(0.000)	(0.067)	(0.000)	(0.001)
At-risk Drinker initial value	0.062	2.421***	0.096	2.441***
	(0.451)	(0.000)	(0.121)	(0.000)
Age	-1.729***	-0.394	-1.600***	-0.747***
	(0.000)	(0.113)	(0.000)	(0.000)
Male			0.177***	0.317***
			(0.000)	(0.000)
Graduate Education	-0.017	-0.108	-0.361***	-0.071
	(0.944)	(0.640)	(0.000)	(0.174)
Vocational Further Education	0.101	0.062**	-0.106**	0.005
	(0.611)	(0.724)	(0.016)	(0.902)
Separated	0.325*	-0.136	0.322**	-0.066
	(0.083)	(0.389)	(0.013)	(0.570)
Divorced	0.214	0.033	0.063	-0.104
	(0.279)	(0.839)	(0.645)	(0.389)
Widowed	0.308	-0.160	0.382*	-0.049
	(0.486)	(0.547)	(0.071)	(0.798)
Never married, cohabiting	0.033	-0.011	0.034	0.025
	(0.863)	(0.948)	(0.812)	(0.844)

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Variables	Men		Pooled	
	(1) Smoker	(2) At-risk Alcohol Use	(3) Smoker	(4) At-risk Alcohol Use
Never married, not cohabiting	0.016	0.210	0.015	0.271*
	(0.939)	(0.244)	(0.925)	(0.053)
Child(ren) in family home	-0.156	-0.077	-0.126	-0.029
	(0.125)	(0.367)	(0.107)	(0.672)
Tobacco Price Index	-0.478*	-0.209	-0.263	-0.080
	(0.066)	(0.295)	(0.167)	(0.601)
Alcohol Price Index	0.16	0.386	-0.319	0.200
	(0.806)	(0.459)	(0.508)	(0.613)
Natural log of Household Annual Disposable Income	0.013	-0.032	0.037	-0.046**
	(0.701)	(0.270)	(0.134)	(0.042)
Smoking Ban	-0.147**	0.058	-0.107**	0.041
	(0.031)	(0.280)	(0.031)	(0.314)
Good Health	0.149**	0.077	0.140***	0.067*
	(0.019)	(0.128)	(0.002)	(0.078)
Fair Health	0.069	0.068	-0.059	0.079
	(0.473)	(0.387)	(0.396)	(0.190)
Poor Health	-0.072	-0.283*	-0.287**	-0.369***
	(0.682)	(0.067)	(0.023)	(0.002)
Major City	-0.017	0.121	-0.100	0.121
	(0.913)	(0.348)	(0.354)	(0.203)
Graduate Education (TA)	-0.453*	0.073		
	(0.087)	(0.768)		
Vocational Further Education (TA)	-0.347	-0.058		
	(0.100)	(0.758)		
Separated (TA)	0.668**	0.851***	0.633***	0.723***

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Variables	Men		Pooled	
	(1) Smoker	(2) At-risk Alcohol Use	(3) Smoker	(4) At-risk Alcohol Use
	(0.016)	(0.001)	(0.001)	(0.000)
Divorced (TA)	0.361	0.047	0.438***	0.287**
	(0.119)	(0.815)	(0.005)	(0.046)
Widowed (TA)	0.300	0.857**	0.023	0.223
	(0.572)	(0.013)	(0.925)	(0.331)
Never married, cohabiting (TA)	0.224	0.112	0.223	-0.101
	(0.325)	(0.590)	(0.189)	(0.528)
Never married, not cohabiting (TA)	0.529**	-0.064	0.514***	-0.059
	(0.031)	(0.766)	(0.004)	(0.718)
Child(ren) in family home (TA)	0.231*	0.050	0.278***	-0.049
	(0.085)	(0.673)	(0.004)	(0.580)
Tobacco Price Index (TA)	-3.833*	7.567***	-0.016	0.036**
	(0.077)	(0.000)	(0.271)	(0.012)
Alcohol Price Index (TA)	4.973*	-8.975***	0.028	-0.050***
	(0.056)	(0.000)	(0.114)	(0.004)
Natural log of Household Annual Disposable Income(TA)	-0.004	0.187***	-0.091**	0.232***
	(0.955)	(0.002)	(0.037)	(0.000)
Smoking Ban (TA)	0.244	-0.887***	0.140	-0.381*
	(0.472)	(0.005)	(0.535)	(0.082)
Good Health (TA)	0.374***	0.038	0.287***	-0.014
	(0.001)	(0.712)	(0.000)	(0.858)
Fair Health (TA)	0.239	-0.096	0.321***	-0.178*
	(0.135)	(0.505)	(0.004)	(0.096)
Poor Health (TA)	0.510*	0.173	0.726***	0.172
	(0.081)	(0.531)	(0.000)	(0.413)

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Variables	Men		Pooled	
	(1) Smoker	(2) At-risk Alcohol Use	(3) Smoker	(4) At-risk Alcohol Use
Major City (TA)	-0.031	-0.273*	0.044	-0.247**
	(0.850)	(0.055)	(0.704)	(0.018)
Intercept	-3.079**	-2.602**	-2.518***	-2.926***
	(0.020)	(0.043)	(0.006)	(0.002)
Unobserved time-variant effects correlation	0.192***		0.149***	
	(0.000)		(0.000)	
Unobserved time-invariant effect variance	0.928***	1.166***	0.875***	1.150***
	(0.000)	(0.000)	(0.000)	(0.000)
Unobserved time-invariant effects correlation	0.107		0.155***	
	(0.102)		(0.000)	
Observations; number of respondents	22,162; 4,508		44,646; 9,309	
Average number of waves in sample	4.9		4.8	
Mean age at initial value	43		44	
Log-likelihood	-9449.23		-16740.344	

Note: TA = time averaged

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A key contribution of this analysis, building on Picone *et al*'s earlier work, is estimation of cross-state dependence between smoking and at-risk drinking equations. Cross-state dependence was estimated to be positive and significant in determining the probability of at-risk alcohol use, but positive and non-significant in determining the probability of smoking participation. An individual's propensity to drink to at-risk levels is influenced by their recent smoking status. These cross-state parameters are fairly small in magnitude, but these are dynamic effects and may be powerful over time. This result is interesting in light of the limited evidence reviewed in Chapter 2, where several studies found changes in tobacco use to have no influence over alcohol use [63, 90, 94]. These studies used longitudinal data, but of only two or three waves, with much smaller samples than used here from different populations, and estimated static equations [63, 90, 94]. Different effects across populations may be expected, but it seems reasonable to speculate that these studies failed to identify cross-behaviour effects, rather than correctly identifying the absence of effect.

The importance of initial behaviour in determining ongoing tobacco and alcohol use status is discernible from the results. The variables *smoker initial value*, *at-risk drinker initial value* and the time-averaged explanatory variables in Table 6 comprise the observed explanatory variables in initial condition equations (23) and (24). The large, positive and highly statistically significant coefficients of *smoker initial value* in columns (1) and (3) and *at-risk drinker initial value* in columns (2) and (4) of Table 6 indicate that the starting points in the dynamic behavioural processes modelled here are very important. Some of the time-averaged variables show a strong predictive effect in Table 6, further highlighting the importance of the start of the dynamic process for behaviour looking forward.

Two further points concerning these initial conditions parameter estimates require note. First, the time averaged price index parameter estimates are large in columns (1) and (2) of Table 6 in comparison to columns (3) and (4). This is due to these variables not being re-scaled prior to estimation for the pooled subsample. The corresponding variable values are around 100 times greater in columns (3) and (4) compared to columns (1) and (2), and so the overall effects are similar. Second, the initial values for smoking and at-risk drinking are the first observation

of each sample member and therefore represent different times in the life cycle across respondents and not the true starting points of the dynamic processes (such as the ages at which purchasing smoking and alcohol become legal). This is a limitation of the data; the mean ages in years of respondents in the male and female estimation samples at which the initial drinking and smoking statuses were reported are 43 and 44, respectively.

Parameter estimates relating to unobserved heterogeneity are reported in Table 6. Unobserved person-specific time-invariant characteristics are shown to play a crucial role in the dynamic processes modelled. The proportion of variance in unobserved errors attributable to unobservable individual heterogeneity is $\sigma_{vj}^2/(1+\sigma_{vj}^2)$ (see equation (20)). For men, this is 45% of unobserved random variation in smoking participation and 53% of random variation in at-risk alcohol use. For the pooled sample, these proportions are 47% and 53%, respectively. Permanent characteristics, such as an addictive nature, seem to be roughly as important as random shocks, such as the death of a loved one, in determining smoking and at-risk drinking status.

Correlation between time-variant unobserved heterogeneity across the two equations is positive, indicating that stochastic shocks which influence the propensity to smoke affect the probability of at-risk drinking in the same direction, and vice versa. This may suggest that a particularly effective smoking cessation campaign may temporarily reduce the propensity to drink to at-risk levels directly, as well as having a potential knock-on effect to future drinking if the campaign leads an individual to quit smoking.

Though positive and highly significant in the pooled sample results, the positive correlation between time-invariant unobserved heterogeneity shown in Table 6 is statistically insignificant for the male subsample, perhaps surprisingly. It is possible that this is due to a lack of variation in the smaller subsample. Time-invariant effects are arguably more interesting from a policy perspective than time-variant effects because while they are difficult to change, if they can be changed for the better then the effect is permanent. The benefit of a smoking cessation intervention which has a high 12-month quit rate may only be temporary

for many if time-enduring characteristics are not affected; Table 6 shows that the starting point and unobserved characteristics are key drivers of dynamic drinking and smoking, even though state dependence is important. If interventions can change these time-enduring characteristics to lower the long-run propensity to smoke, they are far more powerful policy tools. Such an effect is inherently difficult to observe however, and so difficult to speculate on.

Other parameter estimates in Table 6 are of interest from a policy perspective. Propensities to smoke and drink to at-risk levels decrease with age. This is reflective of the falling propensity for these unhealthy behaviours as people move into retirement age and later life generally observed elsewhere [76, 79, 82, 91], though as discussed elsewhere it is not possible to disentangle ageing effects from cohort and period effects without making further identifying assumptions [348]; this result may not be generalisable to future populations. This is important as these results are used to predict long-run behaviour in Chapter 8, as described in Section 5.7.

Being subject to an enclosed public space smoking ban was found to decrease the probability of being a smoker, as expected, though may again be a cohort effect influencing this result. Being in good health, as opposed to very good health, increases the probability of smoking and at-risk drinking participation. Being in poor health, relative to excellent health, reduces the propensity to drink and smoke, though this effect is only prominent in the pooled sample results. These findings are sensible, though because health can influence behaviour and behaviour can also influence health, the direction of causality is not clear.

Increases in tobacco prices were found to reduce the propensity to smoke, as expected, though the parameter estimate for alcohol price index in alcohol equations was, surprisingly, positive. This suggests that alcohol violates the law of demand, but it is far more likely that there is not enough variation in the aggregate price data to estimate an accurate effect.

Among other findings from the model, marital status is found to be a mildly important predictor of smoking status: being separated as opposed to married increases the propensity to smoke. Higher educational attainment is found to reduce the propensity to smoke, while disposable income was negatively

associated with the probability of at-risk drinking, though this effect is significant in the pooled results only.

5.6.2. Attrition and non-response

Results from tests of the significance of 'attrition' variable coefficients are reported in Table 39 and Table 40 of Appendix D. Attrition appears to be inconsequential in determining the probability of 'at-risk' drinking behaviour. By contrast though, the attrition test variables '*number of waves*' and '*all waves*' are statistically significant in smoking participation equations for men and women. The direction of coefficients for these variables suggests that the probability of smoking participation is higher among those with fewer observations in the sample.

It was possible to analyse the potential influence of non-response bias to cross-state dependence estimates in the present application by applying probability weights to the static probit model for the smoking participation decision. Results are reported in Table 41 in Appendix D. Average partial effects (APEs) are reported as well as regressor coefficients, to give quantitative meaning to the differences between weighted and unweighted results. Estimates are fairly similar across weighted and unweighted models for men and women. The APE of 0.016 for '*at-risk drinker last year*' in the unweighted model for males implies that the probability of current smoking is 0.016 higher for those that drank to at-risk levels last year, holding other variables in the model at their sample means. The corresponding APE for the weighted model is 0.019. The magnitude of difference between the weighted and unweighted estimate is small, but the standard error of these APE estimate is also small (0.008 in both unweighted and weighted results), suggesting that the difference is statistically important. Further research into the influence of attrition bias and controlling for such bias in future dynamic analyses of individual-level smoking behaviour using self-reported longitudinal survey data may be of merit.

5.7. Informing projections of behaviour in an economic appraisal model

This econometric analysis was motivated by the need to inform assumptions about long-run patterns of behaviour, and interdependencies between behaviour, in

economic appraisals of competing strategies for smoking cessation or alcohol reduction. Chapters 7 and 8 will report an individual-level simulation model to appraise competing strategies to aid smoking cessation; the results from this chapter informed projections of long-run behaviour in this model. This brief subsection explains how econometric outputs were incorporated into the economic appraisal model.

The first point at which assumptions about behavioural status are needed within the economic appraisal model is when the first person in the model reaches the trial follow-up end point. At this moment, certain characteristics of the person are known. Let us assume that this includes the smoking and drinking status of the person, as well as information on all *observable* variables in equations (26) and (27). The estimated parameter values corresponding to these variables are reported in Table 6.

To estimate the propensity of our person to smoke and drink next year, two further pieces of information are needed. Firstly, assumptions about how observable covariate values change over time are required. Propensity to smoke and drink next year depends on smoking and drinking status last year, but also contemporaneous values for other covariates in the model. Second, estimates of the important unobservable characteristics of our person are needed. While these are not known, using the MSL estimates of $\sigma^2_{\alpha 1}$, $\sigma^2_{\alpha 2}$, ρ_α and ρ_ε, the covariance structure of the unobserved terms and random draws from the uniform distribution across the interval [0,1], sampled estimates of time-invariant and time-variant unobserved effects α_{ji} and u_{jit} can be generated.

With all this information, it is possible to estimate numerical values describing our person's propensities to smoke and drink to an at-risk level the year after final trial follow-up, by inputting the information into the linear equations (26) and (27). If the values produced for y^*_{1it} and y^*_{2it} are greater than 0, our person will be predicted to smoke and drink to at-risk levels.

Future behaviour for this person can be predicted by updating the relevant information, year by year, so that our person's behaviour twenty years further

after trial follow-up will be a function of the pattern of his preceding behaviour and other contributory factors.

In reality, information on many of the person-specific variables in equations (26) and (27) is not routinely collected in trials. In Chapters 7 and 8, assumptions are made in lieu of such knowledge. HILDA estimation sample mean values (Table 44 and Table 45 in Appendix D) were used for all time-varying covariates bar '*age'*, '*male'*, state dependence variables, '*smoking ban*' and price indices. To recap, these time-varying covariates capture income, education status, spousal and parental status and whether individuals live in a major city.

The variable *'smoker last year*' was defined by smoking status at 12 months following smoking cessation treatment, from trial data analysis as described in Chapter 6. Variables for drinking status in the previous year, age and gender were sampled for each simulated person from distributions representative of the target population, as described fully in Chapter 7. The variable '*smoking ban'* was set equal to 1 to reflect contemporary society. Price indices were set to sample means and increased annually in line with average price increases in the UK from 2002 to 2010, based on ONS consumer price index data [349]. Using sample mean values for other covariates is not wholly satisfactory, particularly when many covariates are binary and the model is nonlinear. An alternative would have been to sample from the distributions of each variable for simulated persons in the individual-level model. This could have also enabled correlation between distributions of variables to be accounted for, and may have had some effect upon projected behaviour. The computational burden of this additional complication would have been substantial though, and the effect on final economic appraisal outcomes potentially negligible.

Other variables in equations (26) and (27) not yet accounted for are those variables in the initial conditions equations (23) and (24). It is not possible to observe the starting values for smoking and drinking for individuals in a smoking cessation trial, though they are more likely to start the dynamic process of behaviour as smokers than the general population. In the cost-effectiveness analyses these values were set to attempt to capture the likely values for smoking cessation trial participants. The binary variable '*smoker initial value'* was set to 1

for all simulated individuals, while '*at-risk drinker initial value'* was assumed equal to drinking status upon model entry. Other time-averaged covariates from initial conditions equations (23) and (24) were set equal to HILDA sample means, in the absence of other data. It is not possible to know whether these assumptions best represent the target population, but it is reasoned in Chapter 8 that if these assumptions are applied consistently across treatment comparators in an economic evaluation, the implication for incremental results across comparators is likely small.

Uncertainty around and correlation between parameter estimates in Table 6 is incorporated into the economic appraisal in Chapter 8. Using the mean parameter values and the related covariance matrices reported in Appendix D, Table 47 and Table 48, sampled sets of parameter estimates were drawn from the distribution and used in the probabilistic sensitivity analysis, described further in Chapter 8.

5.8. Discussion

This chapter has presented the first known individual-level bivariate and dynamic investigation of the relationship between alcohol use and tobacco use, using the best available data. The results shown are of interest for numerous reasons, but a key aim of this chapter was to generate output which could be used to project patterns of long-run behaviour in an economic appraisal model for competing strategies to aid smoking cessation. It has been set out how this can be achieved, but it is possible to infer from the results what the impact for appraisal outcomes might be. As Chapter 3 demonstrated, past appraisals have typically made simplistic assumptions about long-term smoking behaviour which imply stability, implicitly favouring strategies with greater short-term effectiveness. Analysis of HILDA data has shown smoking behaviour as a dynamic process to be strongly influenced by historical behaviour and unobserved time-invariant person-specific attributes, suggesting the impact of a smoking cessation intervention will be of less consequence that typically assumed in cost-effectiveness models. The prediction is that short-term effectiveness will be of less importance when these dynamic results are taken into account in Chapter 8 in comparison to Chapter 6, and this will be reflected in smaller incremental differences between outcomes for the strategies under comparison. However, as noted in section 5.6, if smoking

cessation interventions affect the unobserved attributes which are important for smoking propensity, their influence over long-run behaviour will be greater. Comparison of results in Chapters 6 and 8 will highlight the truth of this speculation.

Of the factors that have been shown to influence the decision to smoke, cross-state dependence upon past alcohol status was of minor importance. Cross-state dependence was however found to have a positive influence on the propensity to drink; being a smoker last year increases the probability of being an at-risk drinker next year. Firstly, this further justifies the focus upon treatments for smoking cessation as opposed to strategies to improve alcohol behaviour in subsequent chapters. Secondly, this implies that smoking cessation will have a knock-on effect to alcohol behaviour which increases the expected health benefits of quitting smoking, which should be reflected in Chapter 8 results.

The finding of positive cross-state dependence between alcohol and tobacco use also has potential implications for wider policy. Should strategies to aid smoking cessation include information about the potential knock-on effect of success leading to healthier drinking habits? Would this be viewed by the target audience as an appealing consequence of smoking cessation? These are questions which require further research.

The findings from this analysis are generally consistent with results from previous studies, though little evidence of the interrelated dynamics of smoking and alcohol use exists. Only one previous study has used individual-level panel data to model dynamic alcohol and tobacco use. Picone *et al* estimated equations for alcohol and tobacco consumption using American HRS data and results were generally consistent with those reported here [267]. Importantly though, there were clear differences between Picone *et al* and this study in terms of data (there were two years between each wave of data collection in the HRS) and methods (separate versus joint estimation of equations, analysis of consumption versus participation, treatment of unobserved time-invariant heterogeneity as 'fixed' versus 'random'), which makes it generally difficult to compare results.

Cross-price elasticities have often been used in econometric studies to explain the link between alcohol and tobacco use, perhaps because of the exogeneity of aggregate prices. Elasticity estimates have generally, though not universally [267, 289], suggested complementarity between tobacco and alcohol goods [275, 276, 291, 316]. However, the results presented here have suggested that insufficient variation in aggregate price data may limit the usefulness of such estimates. A similar observation has been made by Tauchmann and colleagues [278]. Though more complex than many of the analyses reviewed in section 5.2, dynamic analyses of variation in individual-level data, such as that presented here, are possible with currently available data and software, and offer far greater explanatory power.

There are limitations to the way alcohol and tobacco use has been modelled in this chapter. Firstly, both tobacco and alcohol behaviours have been modelled as binary participation choices that have health consequences. In the case of smoking, the choice between being a smoker and a non-smoker is real and clearly policy relevant; the NHS Stop Smoking Service exists to help smokers become non-smokers. However, smoking behaviour may have been better modelled as count data. In the case of alcohol use, the difference between drinking to at-risk levels and not *is* relevant to policy, a clear aim of UK alcohol policy is to reduce alcohol consumption levels among hazardous and harmful drinkers to below threshold levels [350], but it is not so clearly a decision that individuals make. In reality, as with smoking and other behaviours, there are multiple decisions which contribute to the observed drinking behaviour of individuals and numerous ways to measure behaviour. The binary decision to drink alcohol is an initial and distinct decision, and the level of alcohol use among drinkers can be measured by average volume or pattern of drinking (binge drinking) [351]. Defining drinking behaviour here as a binary choice between 'at-risk' drinking and not 'at-risk' drinking has precedent [311, 352], but is somewhat simplistic and an improvement would be to treat HILDA drinking data as interval data on frequency and quantity of alcohol use. There was however no software available to jointly estimate two such models and programming would have been complex and beyond the feasible scope of this project. Treating tobacco and alcohol use data as binary choice data at this stage

enabled joint analysis of smoking and alcohol use, within the scope of this research project.

Secondly, there is a practical limitation in the way the initial conditions problem has been treated here. In the dynamic model described by Wooldridge [336], the dynamic process is initiated by the true 'initial' values. This is rarely observed, so the first observed value is used instead. This should be the same point in time for all individuals, for example the age at which smoking becomes legal in a smoking model. In cohort studies that follow individuals of the same age over a life cycle this is often possible, though even in these studies it is not possible to separate age effects and cohort effects. For the HILDA survey, sampling was designed so that the sample reflects the population of households occupying private dwellings in Australia, and so the first observed values for smoking and drinking are at varying ages across individuals in the sample. Of course, it is not possible to separate age effects and cohort effects.

The HILDA Self-Completion Questionnaire does contain some retrospective smoking information, but it is not sufficient to characterise the initial smoking state of respondents [310]. Non-smokers are asked if they ever smoked, but smokers are not asked about initial behaviour. The same is true for alcohol use information. There was some more detailed questioning on smoking behaviour in wave 7 only. In this chapter, the first observed value for each respondent in the sample was used as the initial value. This is a practical approach that has been used in previously published applications of dynamic microeconomic panel data models [327, 353, 354].

Thirdly, using survey panel data to model health-related behaviour creates a potential problem of bias from non-response or attrition. Investigation into the potential implications for the results presented here indicated that non-response is systematically linked to smoking in the HILDA survey, but that any bias in estimates will be small in magnitude. Interestingly, the magnitude of differences in estimates between unweighted and weighted models has been small in a range of health econometrics applications, even when tests have indicated that non-response was linked to the outcome measure [342]. Non-response bias has also

been shown to have limited influence upon results in applications to income dynamics and models of social exclusion [342]. Nevertheless, future research into attrition bias in dynamic analyses of individual-level smoking behaviour using self-reported longitudinal survey data may be of merit.

Aside from the methodological limitations discussed, there is a question of generalisability of the findings here to a UK setting. The predicted probabilities estimated here will be used in the following chapters to quantify the cross-behavioural effects of smoking cessation for at-risk alcohol use, and consequences for health and health care costs in a UK NHS setting. Though the issue is addressed partly by conditioning on variables appropriately when predicting behaviour, there is an outstanding issue of whether cross-state dependence in a sample representative of Australian households can be assumed equivalent to the target population for smoking cessation programmes in the UK. On the one hand, HILDA data was used here in the absence of any equivalent UK data, and the evidence produced here is on the basis of the best available information. On the other hand, evidence of similarities between the sample and the target population strengthen the validity of the outputs from this chapter for this thesis. Recording of demographic characteristics in trials is limited, but recent assessment of 101 attendees at a stop-smoking clinic in London recorded a mean age of 45 years old [355]; only slightly younger than the mean age of 47 of the males in the 'longest run' unbalanced (estimation) sample as shown in Table 44. Mean number of cigarettes smoked per day was higher in the clinic sample (19 cigarettes) than among smokers in the male estimation sample (13 cigarettes). The prevalence of smoking in the estimation sample is almost identical to estimates of smoking prevalence in the UK (22%) [356]. Average weekly units of alcohol in the male estimation sample (12 UK units) was however lower than recent UK estimates for males (16 UK units) [356]. Alcohol consumption might be expected to be higher still among users of smoking cessation services, given the results presented here.

Overall, there are apparent similarities between the sample used to estimate the dynamic link between alcohol and tobacco use in this chapter and the UK general population and those who use smoking cessation services in the UK, but alcohol consumption and consumption of cigarettes among smokers are lower here than

can be expected in UK smoking cessation services. This is a slight limitation, but one that the absence of good UK data made necessary.

5.9. Chapter Summary

The aim of this chapter was to generate evidence on the interrelated dynamics of tobacco and alcohol use, using HILDA survey data in the absence of more appropriate data, which could be used to better inform projections of long-term behaviour in future economic appraisal models. Though there are limitations to the analysis, this aim has been demonstrably achieved. Tobacco and alcohol use are dynamic and interrelated processes and explained not only by past behaviour but various other factors both observed and unobserved in survey data. The results are more generally of interest as a study of the co-dependence and dynamics of two health-related behaviours, in light of very little evidence in this area, and may be of use to policy makers.

The next chapter reports a 'standard practice' cost-utility model for a pharmaceutical agent to aid smoking cessation with potential for use in the UK, replicating the BENESCO model and incorporating potentially unrealistic assumptions about long-run smoking status and links to other behaviour. Chapters 7 and 8 will then respectively describe the methods and results from a *de novo* individual-level economic appraisal model to re-assess the expected cost-utility of this pharmaceutical agent, which incorporates the evidence generate here to project patterns of long-run behaviour.

6. Chapter 6: Standard practice economic appraisal of competing strategies to aid smoking cessation

6.1. Introduction

Chapter 5 demonstrated the interdependence of alcohol use and smoking status, yet in Chapter 6 knowledge of this interdependence is to be temporarily put to one side, as a 'standard practice' economic appraisal of competing strategies to aid smoking cessation is presented. This appraisal follows the methodology of the BENESCO model, used widely in previous applications [357-367], as identified in Chapter 3. Though not all appraisals share the assumptions and structure of the BENESCO model, it is labelled here as 'standard practice' due to the sheer number of applications it has been applied to, and decisions it has informed, including the decision by NICE to recommend the adoption of varenicline as an aid to smoking cessation. The analysis presented here very recently formed the economic analysis for a short review commissioned through the National Institute for Health Research (NIHR) HTA programme [368], showing the BENESCO model to be very much relevant as a standard practice model in this area.

There are three main motivations and objectives driving this chapter. The primary aim is to analyse the results of an economic appraisal of a relevant resource allocation problem using 'standard practice' methods, in order to analyse key drivers of model outputs and assess the importance of inherent and unrealistic modelling assumptions. Secondly, Chapter 6 introduces a contemporary and relevant decision problem for healthcare financers, between competing strategies to aid smoking cessation attempts. Thirdly, Chapter 6 serves to describe methodology to link smoking status to health, HRQoL and costs. These methods will be retained in the BIT model, described in Chapter 7.

Chapter 6 is structured as follows. First, decision problem, methods and data for the model are set out. This includes description of the decision problem, conceptual model, input data and analysis plan. Second, key probabilistic results

are presented, alongside results from probabilistic and various univariate sensitivity analyses. Third, these results and the consequences of limitations of this model are discussed and compared to analyses elsewhere and in anticipation of those from the BIT model, to be demonstrated in subsequent chapters. Fourth, conclusions are drawn.

6.2. Methods

6.2.1. The decision problem

Varenicline was licensed as an aid to smoking cessation in the UK in 2007 and subsequently recommended by NICE following a Single Technology Appraisal (STA) [366]. Varenicline is a synthetic product manufactured by Pfizer; a nicotine receptor partial agonist [368]. These types of drugs aid smoking cessation by abating symptoms of nicotine withdrawal through agonist actions, while countering reinforcing effects of nicotine through antagonist actions [368, 369]. As reported in Chapter 3, varenicline has been shown to have preferential efficacy to licensed pharmaceuticals which work upon smoking receptors in different ways, such as bupropion and NRT.

Cytisine is another nicotine partial receptor agonist, with a similar structure to varenicline [368]. Cytisine is not currently licensed for use in the UK, but has been used as an aid to smoking cessation in Bulgaria (where it is manufactured under the brand name Tabex by Sopharma) and various Eastern European countries for over forty years [370]. That cytisine is not currently UK licensed can be partly attributed to its unusual history of development [370]. Preclinical studies of optimal dosing that would normally form part of the drug development process were not conducted, and until very recently there were no large, placebo-controlled randomised trials that would meet modern regulatory standards [370].

Cytisine is considerably cheaper than varenicline; though prices vary between countries where cytisine is available, the cost of a course of cytisine is generally 10-20% of the cost of a course of varenicline [370]. The NIHR was therefore interested in understanding (i) the estimated cost-utility of cytisine versus varenicline, as an aid to smoking cessation for UK patients and uncertainty around

this estimate, based on current evidence and (ii) the anticipated value of conducting a large scale head to head trial comparing cytisine with varenicline in a UK sample of quit-motivated smokers. The latter was estimated in the NIHR HTA short review using advanced value of information analyses [11, 368, 371]; these results are not reported here. The aims of this chapter are met presenting analyses addressing the problem: 'What is the cost-utility estimate, and uncertainty around this estimate, of cytisine versus varenicline to aid smoking cessation attempts, based on current evidence?'

The economic analysis was focussed on a population on smokers in England and Wales aged 18 years or over who are motivated to quit smoking, and explicitly evaluated the cost-effectiveness of a standard 25 day course of cytisine (six 1.5-mg tablets per day for 3 days (days 1 through 3), five tablets per day for 9 days (days 4 through 12), four tablets per day for 4 days (days 13 through 16), three tablets per day for 4 days (days 17 through 20), and two tablets per day for the final 5 days (days 21 through 25) [372]) with a standard 12 week course of varenicline (500 micrograms once daily for 3 days, increased to 500 micrograms twice daily for 4 days, then 1 mg twice daily for 11 weeks [373].

6.2.2. The conceptual model

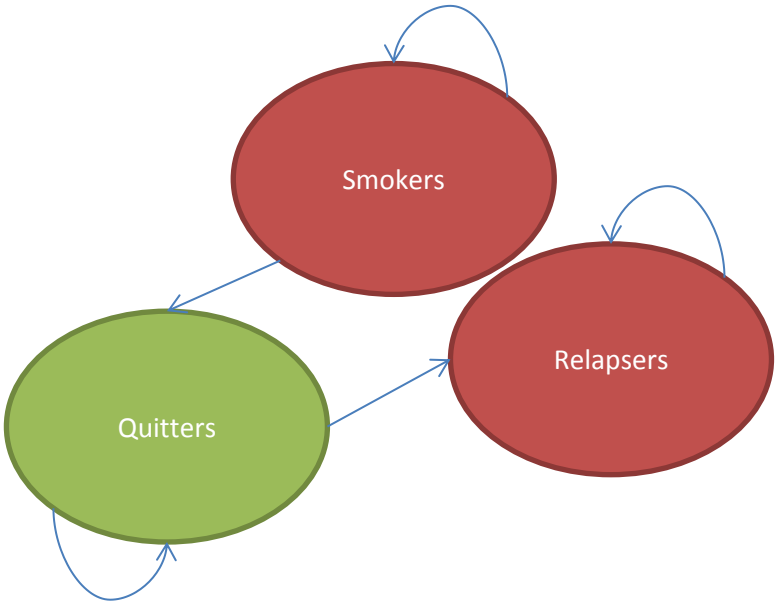
The model structure was based on the existing and widely used BENESCO model [357-367], identified in Chapter 3. The BENESCO model is a state transition model designed to capture important long-term outcomes of smoking cessation treatments.

The model was programmed in Microsoft Excel, uses an annual cycle length and assumes that all smokers die at age 100 years if death had not been simulated at an earlier age. A hypothetical cohort of 10,000 smokers enters the model with each smoker assumed to make a single quit attempt, assisted by either varenicline or cytisine. The distribution of the cohort in terms of gender, age (three age categories are used: 18-34 (years old); 35-64; 65-100) and chronic smoking-related diseases (lung cancer, COPD, CHD and stroke) is assumed to be representative of smokers in England and Wales.

At the start of the model, every cohort member begins in the 'smoker' state. At the end of the first year, a proportion of smokers successfully cease smoking and become 'quitters'; this proportion is determined by the efficacy of the cessation aid treatment received. The model assumes that no further attempts to quit are made and that those who fail to quit remain smokers until death. However, there is a possibility that quitters may relapse and start smoking again in future years. Potential to relapse to smoking is incorporated into the model as a decreasing function of time since cessation, and is independent of cessation treatment (varenicline or cytisine). For the four model cycles following cessation, cohort members are assigned 'recent quitter' status, and risk of relapse is highest. After four cycles without relapse, 'recent quitters' attain 'long-run quitter' status. The annual relapse rate is lower for 'long-run quitters' than 'recent quitters' in the next five cycles, and lower still in subsequent cycles, with this underlying relapse rate continuing for the duration of the model.

At the end of each year, the cohort is distributed into different smoking states (smoker, quitter, relapsed smoker) according to their current smoking state and relapse rates. Figure 10 details the possible transitions between smoking states.

Figure 10: Transitions between smoking states

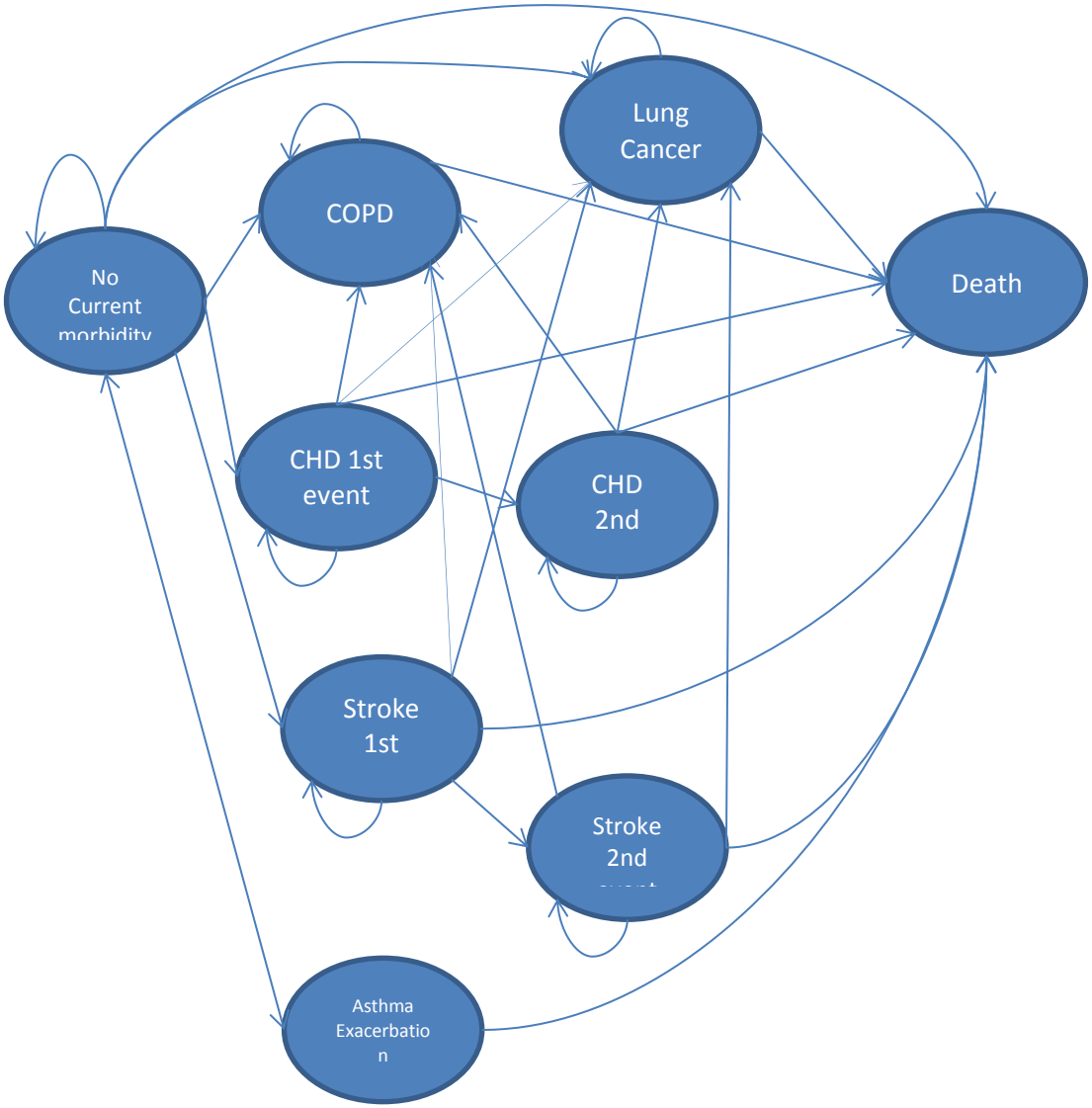


Within these broad smoking states, cohort members are distributed between the following disease states: no current morbidity; lung cancer; COPD; CHD; stroke; and asthma exacerbation. These health states were selected by the authors of the BENESCO model to correspond to the diseases accounting for the greatest morbidity, mortality and cost attributable to smoking [363]. The health states are mutually exclusive, and death is an absorbing state. The probability of transition between disease states at the end of each cycle is dependent on: current disease state; smoking status; age; and gender, as these factors have been shown to be independent determinants of risk.

The model has categorised four of the health states as either acute (CHD and stroke) or chronic (COPD and lung cancer) conditions. Transitions within acute conditions, and within chronic conditions are not allowed, thus it is not possible for a cohort member to experience a CHD event following a stroke. Transitions from acute disease states to chronic disease states are possible, but not from chronic conditions to acute conditions. Asthma exacerbations were transient in nature and assumed to resolve within one year, and could only occur from the no current

morbidity health state. Figure 11 illustrates possible transitions between health states in the model.

Figure 11: Transitions between health states



Each health state is associated with utility and cost values as detailed later. Therefore cohort members accumulate costs and health outcomes each cycle until death. Adverse events are not considered within the BENESCO model framework.

Future costs and benefits were discounted at a rate of 3.5% per annum, and the perspective is that of the UK National Health Service for costs and health effects on

the individual for outcomes, in line with NICE guidance [6]. Attention now turns to parameter values and distributions used in the PSA. Many model inputs are derived from a previous manufacturer STA report [366]. Whilst this is a slight limitation, this is unlikely to affect the key conclusions regarding the relative cost-effectiveness of varenicline and cytisine.

6.2.3. The assumed characteristics of the initial cohort

The distribution of the cohort across gender and age categories at the start of the model was designed to reflect the distribution of smokers in England and Wales. Data on the demographics of the cohort, and prevalence and incidence of diseases among smokers and non-smokers are assumed to be equal to those reported by Pfizer [366]. For convenience these are reproduced in this report together with all cause mortality risk along with the original source (Table 7). The proportion of male and female adults in each of the three age categories was determined from general population data [374]. Smoking prevalence data were applied to this data to calculate the distribution across age and gender groups for a representative sample of 10,000 smokers [375]. Pfizer [366] used interim life tables calculated by the UK Government Actuary's Department for 2002-2004, weighted by population size and averaged to fit the age categories in the model.

Table 7: Data informing demographic distribution of cohort

Data	Original Source	Males 18-34	Males 35-64	Males 65+	Females 18-34	Females 35-64	Females 65+
General population	ONS [374]	6,727,400	11,843,600	4,040,000	6,660,700	12,140,100	5,189,300
Smoking prevalence	ONS [375]	36.20%	27.70%	12.70%	28.00%	28.50%	26.70%
Annual risk of all-cause mortality	Government Actuary's Dept [376]	0.09%	0.47%	4.88%	0.04%	0.30%	3.87%

The prevalence of smoking-related diseases in the cohort was estimated by Pfizer [366] from data on the prevalence of each disease in the general population. Relative risks for the incidence of each disease in the model for smokers were taken from the literature and used to calculate the expected number of cases in the cohort of smokers [377, 378]. These data are reproduced in Table 8.

Table 8: Prevalence of disease in simulated cohort of UK smokers[7]

Data	Original Source	Males 18-34	Males 35-64	Males 65+	Females 18-34	Females 35-64	Females 65+
COPD	Soriano et al [379]	0.00%	1.00%	3.00%	0.00%	1.00%	2.00%
Lung Cancer	Forman et al [380]	0.00%	0.10%	0.70%	0.00%	0.06%	0.24%
History of CHD	ONS [381]	0.00%	1.60%	8.00%	0.00%	1.00%	5.90%
History of Stroke	ONS [381]	0.00%	0.50%	3.00%	0.00%	0.30%	2.00%
Asthma	Asthma UK [382]; Hoskins et al [383]	6.00%	5.00%	6.50%	6.40%	5.30%	5.30%

6.2.4. Transition Probabilities

Annual incidence of disease was estimated by Pfizer [366], divided by age and gender categories, for smokers, 'recent quitters' and 'long-run quitters'. These values relied on estimates from the literature in the majority of cases [382, 384-387], but for COPD there was a lack of available data and incidence was based on mortality data [366]. Office for National Statistics (ONS) data were used to estimate stroke incidence, and these data provided a split between first event and all events [386]. Table 9, Table 10 and Table 11 show estimates for smokers, recent quitters and long-run quitters, respectively, along with original data sources. Relative risks for smokers, short-run quitters and recent quitters were generated from the literature [377, 378] and used to generate absolute probabilities of incidence. As can be seen, the incidence of smoking-related diseases is at least as high in smokers compared with recent quitters, and in recent quitters compared with long-run quitters.

[7] Pfizer 366. Pfizer UKL. Varenicline: Single Technology Appraisal Submission2007. were not consistent in reporting to a set number of decimal places or significant figurers. In this report, for consistency, prevalence, incidence and mortality data, though taken from the manufacturer submission, are reported to at least 2 decimal places.

Table 9: Annual incidence of diseases in smokers by age and gender category

Data	Original Source	Males 18-34	Males 35-64	Males 65+	Females 18-34	Females 35-64	Females 65+
COPD	Pfizer [366]	0.00%	0.02%	0.55%	0.00%	0.02%	0.44%
Lung Cancer	ONS [386]	0.00%	0.10%	1.00%	0.00%	0.08%	0.50%
CHD (first non-fatal)	British Heart Foundation [384]	0.00%	0.10%	1.00%	0.00%	0.05%	0.86%
CHD (subsequent non-fatal)	Volmink et al [387]	0.00%	0.19%	1.74%	0.00%	0.05%	1.18%
Stroke (first non-fatal)	ONS [385]	0.00%	0.26%	0.92%	0.00%	0.20%	0.74%
Stroke (subsequent non-fatal)	ONS [385]	0.00%	0.35%	1.55%	0.00%	0.28%	1.33%
Asthma exacerbation	Asthma UK [382]	0.08%	0.05%	0.07%	0.08%	0.05%	0.06%

Table 10: Annual incidence of diseases in 'recent quitters' by age and gender category

Data	Original Source	Males 18-34	Males 35-64	Males 65+	Females 18-34	Females 35-64	Females 65+
COPD	Pfizer [366]	0.00%	0.02%	0.40%	0.00%	0.01%	0.43%
Lung Cancer	ONS [386]	0.00%	0.04%	0.43%	0.00%	0.03%	0.20%
CHD (first non-fatal)	British Heart Foundation [384]	0.00%	0.08%	0.81%	0.00%	0.02%	0.71%
CHD (subsequent non-fatal)	Volmink et al [387]	0.00%	0.12%	1.39%	0.00%	0.02%	0.97%
Stroke (first non-fatal)	ONS [385]	0.00%	0.11%	0.61%	0.00%	0.08%	0.55%
Stroke (subsequent non-fatal)	ONS [385]	0.00%	0.14%	1.03%	0.00%	0.11%	1.00%
Asthma exacerbation	Asthma UK [382]	0.05%	0.05%	0.06%	0.06%	0.05%	0.06%

Table 11: Annual incidence of diseases in 'long-run quitters', by age and gender category

Data	Original Source	Males 18-34	Males 35-64	Males 65+	Females 18-34	Females 35-64	Females 65+
COPD	Pfizer [366]	0.00%	0.02%	0.05%	0.00%	0.00%	0.04%
Lung Cancer	ONS [386]	0.00%	0.04%	0.43%	0.00%	0.03%	0.20%
CHD (first non-fatal)	British Heart Foundation [384]	0.00%	0.05%	0.68%	0.00%	0.01%	0.50%
CHD (subsequent non-fatal)	Volmink et al [387]	0.00%	0.07%	1.16%	0.00%	0.02%	0.69%
Stroke (first non-fatal)	ONS [385]	0.00%	0.11%	0.61%	0.00%	0.05%	0.46%
Stroke (subsequent non-fatal)	ONS [385]	0.00%	0.00%	0.01%	0.00%	0.00%	0.01%
Asthma exacerbation	Asthma UK [382]	0.05%	0.05%	0.06%	0.06%	0.05%	0.05%

Annual mortality probability by condition was estimated by Pfizer [366] for smokers, recent quitters and long-run quitters, by age and gender specific category. Mortality associated with asthma exacerbation was assumed to equal all-cause mortality (Table 7). Mortality for chronic diseases, COPD and lung cancer, is the probability of death from these diseases given the disease state is present. Mortality from acute events, CHD and stroke, is the probability of a fatal event that differs by smoking status, age and gender. Table 12, Table 13 and Table 14 show disease-specific mortality estimates for smokers, recent quitters and long-run quitters, respectively, as reported by the manufacturer's submission for the NICE varenicline STA [366], along with the original data sources. Relative risks of mortality for smokers, recent quitters and long-run quitters from the literature were used [377, 378]. The probability of smoking-related mortality is equivalent or lower for recent quitters compared with smokers and for long-run quitters relative to recent quitters.

Table 12: Annual mortality for smokers, by age and gender category

Data	Original Source	Males 18-34	Males 35-64	Males 65+	Females 18-34	Females 35-64	Females 65+
COPD	ONS [374]	0.00%	0.98%	10.12%	0.00%	0.70%	9.16%
Lung Cancer	ONS [374]	0.00%	26.89%	47.69%	0.00%	40.48%	75.35%
CHD (first event fatal)	British Heart Foundation [384]	0.00%	0.10%	0.81%	0.00%	0.04%	0.69%
CHD (subsequent event fatal)	ONS [374]	0.00%	0.15%	1.39%	0.00%	0.04%	0.94%
Stroke (first event fatal)	ONS [374]	0.00%	0.02%	0.30%	0.00%	0.02%	0.38%
Stroke (subsequent event fatal)	ONS [374]	0.00%	0.03%	0.50%	0.00%	0.03%	0.56%

Table 13: Annual mortality for 'recent quitters', by age and gender category

Data	Original Source	Males 18-34	Males 35-64	Males 65+	Females 18-34	Females 35-64	Females 65+
COPD	ONS [374]	0.00%	0.98%	10.12%	0.00%	0.70%	9.16%
Lung Cancer	ONS [374]	0.00%	26.89%	47.69%	0.00%	40.48%	75.35%
CHD (first event fatal)	British Heart Foundation [384]	0.00%	0.06%	0.65%	0.00%	0.02%	0.56%
CHD (subsequent event fatal)	ONS [374]	0.00%	0.09%	1.12%	0.00%	0.02%	0.78%
Stroke (first event fatal)	ONS [374]	0.00%	0.01%	0.20%	0.00%	0.01%	0.28%
Stroke (subsequent event fatal)	ONS [374]	0.00%	0.01%	0.33%	0.00%	0.01%	0.42%

Table 14: Annual mortality for 'long-run quitters', by age and gender category

Data	Original Source	Males 18-34	Males 35-64	Males 65+	Females 18-34	Females 35-64	Females 65+
COPD	ONS [374]	0.00%	0.98%	10.12%	0.00%	0.70%	9.16%
Lung Cancer	ONS [374]	0.00%	26.89%	47.69%	0.00%	40.48%	75.35%
CHD (first event fatal)	British Heart Foundation [384]	0.00%	0.04%	0.54%	0.00%	0.01%	0.40%
CHD (subsequent event fatal)	ONS [374]	0.00%	0.06%	0.93%	0.00%	0.01%	0.55%
Stroke (first event fatal)	ONS [374]	0.00%	0.01%	0.20%	0.00%	0.01%	0.24%
Stroke (subsequent event fatal)	ONS [374]	0.00%	0.01%	0.33%	0.00%	0.01%	0.35%

6.2.5. Relapse rates

In the previous manufacturer's submission for the NICE varenicline STA [366], the annual probability of relapse to smoking for the first five years following cessation was calculated from a longitudinal US four year follow-up study of a health improvement initiative in the workplace (n=1143) [388]. The probability used was criticised by the Evidence Review Group, as it was incorrectly derived from baseline length of abstinence data [389]. Whilst it was possible to estimate annual probability of relapse from this study, using follow-up data for the sub-sample of participants that had been abstinent for one to two years at baseline, this sub-sample comprises only 79 participants.

A more recent study has used BHPS data to analyse relapse to smoking (n=1578) [390]. The article shows numbers relapsing each year among those reporting non-smoking for at least one year having previously reported smoking, for duration of cessation of up to ten years. These data were used to calculate the annual relapse probability for short-run quitters (<5 years since quit) and a proportion of long-run quitters (more than five years but less than a decade post-quit). Data on annual relapse probability ten or more years post-cessation are scarce and in the

absence of more robust data, the same data as used by Pfizer [366] were employed here [391].

Table 15 shows the probabilities of relapse used in the model. The probability of relapse in the first ten years post 1 year of cessation is higher than estimates used in some previous models [357-359, 362, 366] but is in line with other research which suggests that around half of those abstinent at one year will relapse to smoking in the next seven years [392, 393]. The annual probability of relapse after ten years of abstinence was assumed to be 1% in the STA submission and several other applications of the BENESCO model [357-359] which all based their estimate on a longitudinal study [391]. The authors for this longitudinal study report that '*the (annual) rate of smoking relapse…fell to less than 1% after ten years of abstinence*'. Using the data reported in the study [391], the annual probability of relapse according to the data is much lower than 1%. Uncertainty around relapse rates is modelled in this report as a beta distribution, using event data from the original studies [390, 391].

Table 15: Relapse probabilities, by duration of abstinence

Data	Original Source	Mean probability	95% CI	Distribution over relapse category time period [8]
Annual relapse probability, >1 & <5 years post cessation (time period 4 years)	Hawkins et al [390]	0.129	[0.117, 0.141]	Beta (395, 535)
Annual relapse probability, >=5 & <10 years post cessation (time period 5 years)	Hawkins et al [390]	0.0331	[0.0230, 0.0452]	Beta (33, 180)
Annual relapse probability, >10 years post cessation (time period 26 years)	Krall et al [391]	0.00112	[0.000402, 0.00153]	Beta (9, 390)

[8] Parameter values correspond to total time period in 'Data' column: 4 years for relapse 1-5 years post cessation , 5 years for relapse 6-10 years post-cessation and 26 years for relapse over 10 years post cessation (reflecting the follow-up period of Krall (2002[99])). Instantaneous relapse rates were first calculated from the data, and then converted to one year probabilities.

6.2.6. Costs

Costs included in the model were costs relevant to disease states and intervention costs. The mean costs for COPD, CHD and asthma are those reported in Hind *et al* [394]. The source for COPD cost is the average direct cost of treatment, weighted by severity, taken from a study estimating burden of disease in the UK [395]. The annual cost of lung cancer was taken from a NICE Rapid Review [396], sourced from a UK epidemiology study [397]. The annual patient cost for CHD is an estimate of the aggregate cost of CHD to the NHS [398], divided by estimated prevalence. The cost of asthma exacerbations represented a mixture of the estimated cost of an A&E attendance and NHS reference cost of inpatient attendance, with the ratio of A&E to inpatient admissions estimated taken from a UK an asthma risk factor analysis [383]. Costs for stroke were taken from a recent NIHR HTA report [399], and incorporates the one-off and ongoing costs of stroke, and the reported difference in costs and prevalence of dependent and independent patient states following a stroke incident [400]. All costs have been adjusted for inflation to 2011/12 prices [401].

Uncertainty around cost estimates were incorporated into the probabilistic analysis. In the absence of data, the standard errors for COPD, lung cancer, CHD and asthma exacerbation were assumed to be 10% of the mean estimate. These data were assumed to follow a gamma distribution, as is common practice for cost data [10]. Confidence intervals around costs following stroke events reported in the recent NIHR commissioned Technology Assessment Report [399] informed the uncertainty around mean costs for stroke, which was assumed to fit a normal distribution. Table 16 reports the source, summary estimates and distributions used for the disease state costs used in the model.

Table 16: Disease state annual costs

Data	Original Source	Mean Cost (£)	95% CI	Distribution
COPD	Britton [395]	971.31	[780.93, 1161.69]	Gamma (100, 9.71)
Lung Cancer	Sanderson & Spiro [397]	6,524.02	[5245.31, 7802.72]	Gamma (100, 65.24)
CHD (non-fatal event)	McMurray et al [398]	1,162.5	[934.45, 1390.05]	Gamma (100, 11.62)
Stroke (non-fatal event)	Simpson et al [399]	5,484.31	[4996.99, 5970.85]	0.741*[Normal(576.51,15.74) + Normal(3398.40,175.83)] + 0.259*[Normal(3010.17,66.21) + Normal(6792.55,345.70)]
Asthma Exacerbation	Hoskins et al [383]	1,162.25	[846.73, 1259.56]	Gamma (100, 10.53)

Intervention costs comprised the cost of the drug regimen. Costs of brief counselling and support of a health professional are also likely to occur, but not likely to differ between drug treatments, thus not impacting relative cost-utility, and were not included in the economic analysis. For the comparator intervention, standard treatment with varenicline, British National Formulary (BNF) data on dosage and pricing were used [373]. The cost of treatment is the cost of a starter pack covering the first two weeks of tapered treatment (£27.30) plus the cost of ten weeks at full dose (5 x £27.30), £163.80 in total. The cost of cytisine treatment within a UK setting is not determined. The manufacturers of cytisine were contacted but no reply was received. In the absence of firm evidence, it is strongly suspected that a course of cytisine will be significantly cheaper than a standard course of varenicline [370, 402]. A previous model of the costs and effects of cytisine for smoking cessation assumed treatment costs to be US$10 per smoker [402]. As of March 2013, it was possible to buy Tabex (active ingredient cytisine) online in the

UK for £16.79 for 100 1.5mg tablets [403], which represents approximately a standard course, and this cost is used in the model. Table 17 shows the treatment costs used in the model.

Table 17: Treatment costs

Data	Original Source	Total Cost (£)
Cytisine Treatment Cost	Assumption	16.79
Varenicline Treatment Cost	BNF [373]	163.80

6.2.7. Utilities associated with health states

Baseline utility for smokers with no current comorbidity were taken from the general population utility profile estimated by Ara and Brazier using HSE data [404]. These data are a function of age and gender. Disease-specific utility values for smoking-related diseases are the same as reported by the manufacturer submission team [366]. For lung cancer utility [405], asthma exacerbation utility [406] and a second non-fatal stroke event utility [407], a utility multiplier associated with the disease was estimated by comparing the reported utility value with the expected value for a person of the same age within the general population, assuming that age-specific values from the UK were applicable for all populations. The average ages of the samples from which utility values were drawn were 62 years, 49 years and 65 years for lung cancer, asthma exacerbations and a second non-fatal stroke, respectively. The mean ages of the population for which the utilities were provided for a first non-fatal stroke event [408], COPD [409] and following any CHD event [410], were not reported. For these disease states, an average age of 60 years is assumed with the sensitivity of the results to this assumption is explored by altering baseline utility estimates for these diseases to correspond to ages 50 and 70 years, respectively.

Disease state utility was determined using a multiplicative approach, i.e. baseline utility is multiplied by an estimate of the impact of the disease. Table 18 displays

the mean utility values for health states in the model. Thus a male aged 40 years with lung cancer would have an estimated utility of 0.44 (0.88 x 0.50).

Table 18: Health state mean utility values

Health State	Utility Source	Mean Age	Mean Utility
Age- and gender-specific utility values			
No current morbidity (NCM) Males 18-34	Ara [404]	26.5	0.94
NCM Males 35-64	Ara [404]	49	0.88
NCM Males 65-100	Ara [404]	82.5	0.72
NCM Females 18-34	Ara [404]	26.5	0.92
NCM Females 35-64	Ara [404]	49	0.86
NCM Females 65-100	Ara [404]	82.5	0.70
Disease-specific utility multipliers			
Lung Cancer	Trippoli et al [405]	62	0.50
COPD	Spencer et al [409]	60	0.63
CHD	Hay & Sterling [410]	60	0.63
Stroke 1st Event	Tengs & Lin [408]	60	0.62
Stroke 2nd Event	Gage [407]	65	0.12
Asthma Exacerbation	Szende [406]	49	0.45

Uncertainty around utility estimates is explored in the probabilistic analysis. Normally distributed error terms from OLS regressions used to predict baseline utility by Ara and Brazier [404] represent uncertainty around utility inputs and were used to explore uncertainty in model outputs as part of the PSA. Uncertainty in the values reported for each health state was not considered and therefore the true uncertainty will be underestimated.

6.2.8. Intervention effectiveness

The NIHR HTA short review included a systematic review and network meta-analysis of effectiveness data for varenicline and cytisine [368]. Sixteen studies comparing pairs, triplets or quintuplets of interventions informed the meta-analysis, which covered eight drug regimens (NRT patch, cytisine 1.5mg 6 times daily, varenicline 0.3mg once daily, varenicline 1.0mg once daily, varenicline 0.5mg

twice daily, varenicline 1.0mg twice daily, bupropion 150mg twice daily, placebo) [368].

The absolute probabilities of cessation at one year for interventions were generated by combining the results of the network meta-analysis with an estimate of the placebo response, as described in the short review [368]. The median and mean probability of one-year continuous abstinence for cytisine and varenicline and 95% credible intervals (CrI) are shown in Table 19. The wide credible intervals are reflective of uncertainty around the baseline (placebo) effect. There is much less uncertainty about the treatment effects and the order of the effectiveness of the two treatment comparators. The probability that cytisine 1.5mg was the most effective treatment of the eight compared in the meta-analysis was 0.86. When only cytisine 1.5mg and varenicline 1mg bid are compared, the probability that cytisine is the most effective treatment was estimated to be 0.90. The 95% credible interval around the difference between effectiveness of the interventions (probability of quit with cytisine minus probability of quit with varenicline) includes zero [-0.048, 0.389].

Table 19: Absolute probability of one year continuous cessation

	Median	**Mean**	**95% CrI**
Cytisine, One-year Continuous Abstinence Probability	0.394	0.449	[0.040, 0.998]
Varenicline, One-year Continuous Abstinence Probability	0.257	0.330	[0.026, 0.958]

Discussion of key assumptions

The BENESCO modelling approach involves several assumptions, as noted throughout this chapter. A key assumption implicit in the model is that cohort members can only quit after treatment for smoking cessation, within the first model cycle, and at no other point until death. In reality, smokers who are willing to quit but fail during one attempt will have a probability of successfully quitting at a later stage in their lives. This assumption is likely to favour interventions with greater efficacy. If the 1-year probability of cessation is significantly higher for one treatment than another, that treatment will have greater health outcomes across

the cohort over the lifetime horizon. This assumption is a feature of all previous applications of the BENESCO model [357-367].

The economic model has relied in part on input data from a previous manufacturer's submission for the NICE varenicline STA [366]. It is not known if these inputs are the best available as (i) at least five years have elapsed since these data were identified and (ii) identification of input studies was not always clearly reported. The majority of cost, utility and relapse data were from the UK, but a proportion of these data were from non-UK studies [377, 378, 391]. The model assumes transferability of these data to a UK NHS setting. Additionally, the model assumes treatments are not associated with adverse events.

6.2.9. Analysis of uncertainty

The uncertainty around key parameter estimates was modelled by the use of probability distributions which allowed PSA to be undertaken. Ten thousand draws from distributions of treatment effectiveness, health state utility, disease costs and relapse probabilities were used as model inputs. Furthermore, univariate sensitivity analysis was performed to ascertain the key drivers of model outputs. Value of information analyses was also undertaken. This involved the calculation of the expected value of perfect information (EVPI) [411].

6.3. Results

6.3.1. Mean outcomes associated with each treatment

The results of the PSA are presented as the primary results of interest, as, unlike deterministic estimates, they take into account the distributions of input parameters and interaction between parameters, and thus are the more accurate estimates. Table 20 shows the primary results of the PSA analysis: per smoker total discounted costs, LYs and QALYs for the two treatments. Cytisine is expected to be less costly and more effective than varenicline, and so can be said to dominate varenicline, based on the expected values.

Table 20: Mean Per-Smoker Discounted Total and Incremental Costs, Life Years and QALYs from the economic analysis

Treatment	Costs		Life Years		QALYs	
	Total	Incr.	Total	Incr.	Total	Incr.
Cytisine	£ 4973	-£251	17.53	0.03	14.55	0.03
Varenicline	£ 5225		17.50		14.52	

Figure 12 presents the cost-effectiveness acceptability curves [412] for the two treatments. At any threshold willingness to pay of up to £100,000 per QALY gained, cytisine was the optimal intervention in over 90% of the simulations within the PSA. This reflects the higher costs associated with varenicline treatment. As the willingness to pay increases, the probability that cytisine is preferable falls and the likelihood varenicline is optimal rises. Given that cytisine was estimated to be the more effective treatment in 90% of simulations the value for cytisine on the cost-effectiveness acceptability curve will asymptote at 90%.

Figure 12: Cost-effectiveness acceptability curves for cytisine and varenicline

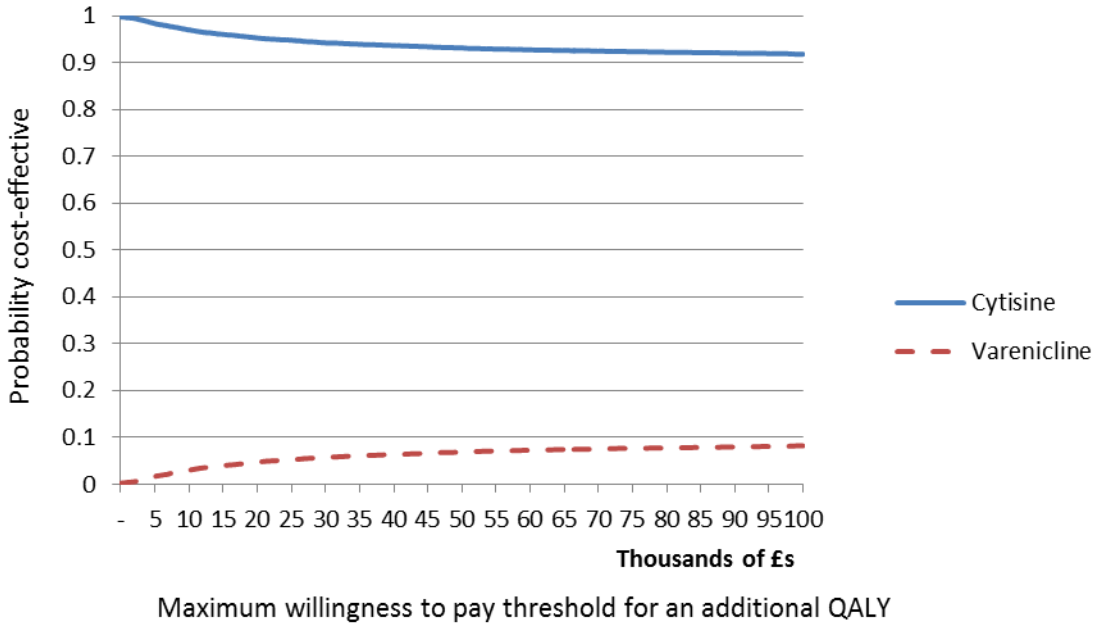
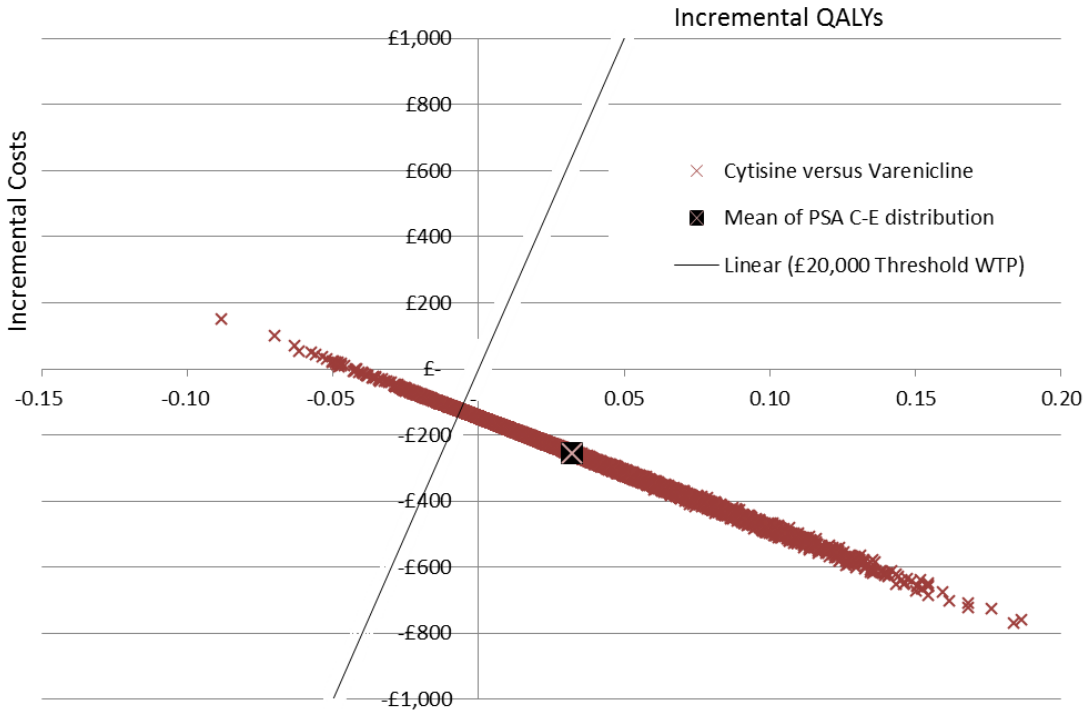


Figure 13 shows the distribution of the 10,000 estimated cost-effectiveness pairs. There is clear correlation between incremental costs and incremental QALYs: health outcomes are important in determining long-term costs. The wide range of per-person health and cost outcomes is reflective of the uncertainty around the relative effectiveness of cytisine and varenicline, as illustrated by the univariate sensitivity analyses.

Figure 13: Scatter plot of results from 10,000 PSA runs



6.3.2. Univariate sensitivity analyses

Table 21 details the results from the univariate sensitivity analyses. In all the analyses, bar one, the conclusion that cytisine dominates varenicline is upheld. The exception was in altering the relative efficacies of varenicline and cytisine. This analysis was operationalised by ranking the output from the network meta-analysis based on the value in the differences of the absolute quit rates between cytisine and varenicline and using the 2.5th and 97.5th percentile. When using the value most favourable to varenicline an additional 0.01 QALYs at an additional cost of £103 were estimated for varenicline versus cytisine, resulting in a cost per QALY gained of just under £8,000 for varenicline which would be typically seen as cost-

effective under typical NICE thresholds [6], thus leading to a different adoption decision to the baseline analysis.

The assumed treatment cost for cytisine is lower than that for varenicline, but the cytisine cost estimate if adopted for use within the NHS is uncertain. In a threshold analysis it was estimated that the price of the cytisine regimen would have to rise to over £250 (from an estimate of £16.79, a greater than 14-fold rise) for the total expected lifetime cost with cytisine treatment to equal the total expected lifetime cost with varenicline treatment.

Table 21: Univariate sensitivity analysis result, per smoker discounted outcomes

Variable	Sensitivity analysis	Treatment	Costs		LYs		QALYs	
			Total	Incr.	Total	Incr.	Total	Incr.
Baseline		Cytisine	£ 4,973	-£251	17.53	0.03	14.55	0.03
		Varenicline	£ 5,224		17.50		14.52	
COPD utility	Assumed age of study sample 50 years	Cytisine	£ 4,973	-£251	17.53	0.03	14.56	0.03
		Varenicline	£ 5,224		17.50		14.53	
	Assumed age of study sample 70 years	Cytisine	£ 4,973	-£251	17.53	0.03	14.54	0.03
		Varenicline	£ 5,224		17.50		14.50	
CHD utility	Assumed age of study sample 50 years	Cytisine	£ 4,973	-£251	17.53	0.03	14.57	0.03
		Varenicline	£ 5,224		17.50		14.54	
	Assumed age of study sample 70 years	Cytisine	£ 4,973	-£251	17.53	0.03	14.52	0.03
		Varenicline	£ 5,224		17.50		14.49	
Stroke 1st event utility	Assumed age of study sample 50 years	Cytisine	£ 4,973	-£251	17.53	0.03	14.57	0.03
		Varenicline	£ 5,224		17.50		14.53	
	Assumed age of study sample 70 years	Cytisine	£ 4,973	-£251	17.53	0.03	14.53	0.03
		Varenicline	£ 5,224		17.50		14.50	
Cytisine Cost	Double	Cytisine	£ 4,990	-£234	17.53	0.03	14.55	0.03
		Varenicline	£ 5,224		17.50		14.52	

Variable	Sensitivity analysis	Treatment	Costs		LYs		QALYs	
			Total	Incr.	Total	Incr.	Total	Incr.
COPD cost	Upper 95% CI value	Cytisine	£ 5,037	-£252	17.53	0.03	14.55	0.03
		Varenicline	£ 5,289		17.50		14.52	
	Lower 95% CI value	Cytisine	£ 4,909	-£250	17.53	0.03	14.55	0.03
		Varenicline	£ 5,159		17.50		14.52	
Lung Cancer cost	Upper 95% CI value	Cytisine	£ 5,062	-£254	17.53	0.03	14.55	0.03
		Varenicline	£ 5,317		17.50		14.52	
	Lower 95% CI value	Cytisine	£ 4,883	-£248	17.53	0.03	14.55	0.03
		Varenicline	£ 5,132		17.50		14.52	
CHD event cost	Upper 95% CI value	Cytisine	£ 5,126	-£252	17.53	0.03	14.55	0.03
		Varenicline	£ 5,378		17.50		14.52	
	Lower 95% CI value	Cytisine	£ 4,820	-£250	17.53	0.03	14.55	0.03
		Varenicline	£ 5,070		17.50		14.52	
Stroke event cost	Upper 95% CI value	Cytisine	£ 5,273	-£258	17.53	0.03	14.55	0.03
		Varenicline	£ 5,531		17.50		14.52	
	Lower 95% CI value	Cytisine	£ 4,672	-£244	17.53	0.03	14.55	0.03
		Varenicline	£ 4,916		17.50		14.52	
Asthma event cost	Upper 95% CI value	Cytisine	£ 4,975	-£251	17.53	0.03	14.55	0.03
		Varenicline	£ 5,226		17.50		14.52	
	Lower 95% CI value	Cytisine	£ 4,971	-£251	17.53	0.03	14.55	0.03
		Varenicline	£ 5,222		17.50		14.52	
Relapse probability 1 to 4 years	Upper 95% CI value	Cytisine	£ 4,992	-£246	17.52	0.03	14.54	0.03
		Varenicline	£ 5,238		17.49		14.51	
	Lower 95% CI value	Cytisine	£ 4,954	-£256	17.54	0.04	14.55	0.03
		Varenicline	£ 5,210		17.50		14.52	
Relapse probability 5 to 9 years	Upper 95% CI value	Cytisine	£ 4,989	-£247	17.52	0.03	14.54	0.03
		Varenicline	£ 5,236		17.49		14.51	
	Lower 95% CI value	Cytisine	£ 4,959	-£255	17.53	0.03	14.55	0.03
		Varenicline	£ 5,214		17.50		14.52	

Variable	Sensitivity analysis	Treatment	Costs		LYs		QALYs	
			Total	Incr.	Total	Incr.	Total	Incr.
Relapse probability 10+ years	Upper 95% CI value	Cytisine	£ 4,975	-£251	17.53	0.03	14.55	0.03
		Varenicline	£ 5,225		17.50		14.52	
	Lower 95% CI value	Cytisine	£ 4,972	-£252	17.53	0.03	14.55	0.03
		Varenicline	£ 5,223		17.50		14.52	
Difference between treatment effectiveness (cytisine minus varenicline)	Upper 95% CrI value	Cytisine	£ 4,743	-£504	17.60	0.12	14.62	0.11
		Varenicline	£ 5,246		17.49		14.51	
	Lower 95% CrI value	Cytisine	£ 5,206	-£103	17.45	-0.01	14.48	-0.01
		Varenicline	£ 5,309		17.47		14.49	

6.3.3. Calculation of the EVPI

EVPI is defined as the value of eliminating all uncertainty around the adoption decision. The value is determined by both (i) the probability that a wrong adoption decision will be made and (ii) the costs of forgoing the optimal treatment strategy.

In order to calculate the EVPI, an estimate of the number of people affected by the more accurate information was required. A recent ONS report estimated that 21% of the UK adult population smoke, around 10 million people, and the same report found that 63% of smokers want to quit smoking [356]. If even half of those with a desire to quit attempt assisted cessation while the choice between cytisine and varenicline is relevant, the adoption decision will affect more than 3 million UK smokers. Elsewhere, it has been estimated that 800,000 smokers currently access Stop Smoking Services in England each year [413], supporting the notion that 3 million smokers could be affected in England and Wales.

Analysis of US data from the 2003 Tobacco Use Cessation Supplement to the Current Population Survey found of those attempting to quit (43.5% of all smokers), one third (32.2%; 14.0% of all smokers) used medication [414]. The proportion of attempted quitters using medication was lower in the UK at the turn of the century, but increasing as NRT and bupropion became available on prescription [415]. However, a study into the reasons smokers shy away from medications suggests that perceived effectiveness has lessened use of smoking

cessation drugs in the past [416]. The high efficacy of the dopamine-inhibitors cytisine and varenicline, in comparison to NRT, will likely attenuate this effect. Ease of access has also been cited as a factor [416]. This all suggests that with a focus on implementation in UK stop smoking services, to overcome these barriers, the proportion of quit attempts assisted by medication could rise significantly in the next ten years. The figure of 3 million affected smokers is considered credible, but the EVPI was also calculated with the assumption of 1 million smokers affected.

The INB of cytisine compared with varenicline was calculated per smoker for each of the PSA runs for willingness to pay thresholds for an additional QALY of £20,000 and £30,000. In over 90% of PSA runs the INB was positive indicating that varenicline was not cost-effective. However, in the remainder of the PSA runs the value was negative, indicating that varenicline was cost-effective. The maximum INB was calculated as the sum of all positive INB, divided by the number of PSA runs (10,000). The expected INB was calculated as the sum of all INB, divided by the number of PSA runs. The EVPI was calculated as the difference between maximum INB and expected INB. This value was £11.71 per smoker assuming a willingness to pay of £20,000 per QALY gained, and £19.99 per smoker assuming a willingness to pay of £30,000 per QALY.

Whilst these are small EVPI values per person the value becomes much greater when multiplied by 3 million to represent the likely population affected by the decision resulting in EVPI values of £35.13 million and £59.96 million at a willingness to pay levels per QALY of £20,000 and £30,000 respectively. Even with a conservative value of only 1 million smokers affected by the decision and with willingness to pay £20,000 for an additional QALY, the EVPI was £11.71 million.

6.4. Discussion

PSA outputs from the model presented in this chapter suggest that cytisine for smoking cessation will produce greater mean life years and QALYS, and lower mean lifetime costs than varenicline, which was previously considered to be the most cost-effective smoking cessation treatment strategy. At a willingness to pay threshold of £20,000 for an additional QALY, the probability that cytisine treatment is preferable to varenicline treatment is 0.95, and this probability does not fall below 0.9. Despite this, the value of further information on the relative

effectiveness of the two strategies is high because of the very large numbers of smokers assumed to be affected by the further information.

A key driver of the dominance of cytisine treatment over varenicline treatment in this economic analysis is the relative effectiveness of cytisine versus varenicline, as shown in the univariate sensitivity analysis. In summary, the treatment which generates the greatest number of quitters will have the best long-term health-related outcomes as efficacious treatment also has the impact of reducing costs associated with longer-term conditions associated with smoking. If treatment costs were equal for varenicline and cytisine, the probability that cytisine is the optimal choice is 0.9 (at any willingness to pay value), reflecting the 0.9 probability that cytisine has the greater 1-year continuous cessation probability.

It was not possible to validate the economic model outputs against results in the STA report, as the number in the simulated cohort in the latter was not reported and so per smoker values are unknown [389]. Other previous applications of the BENESCO model have used non-UK populations and parameter inputs, making comparison of total LYs, QALYs and costs difficult [357-367]. However, results across these studies and here have been similar, in that the intervention with the greatest effectiveness (short-term cessation probability) has consistently had the greatest cost-utility.

The key limitation of the model structure used is the imposed assumption of no underlying quit rate, among failed quitters or relapsed smokers, which is likely to favour treatments with higher effectiveness. Other UK analyses of the cost-effectiveness of smoking cessation interventions have assumed underlying quit rates of between 1% and 2.5% [392, 396, 417], but these estimates originated from a study that used now dated cross-sectional data [418]. In each of these studies, unlike here, the most efficacious strategy had the highest treatment cost, but like here, the strategy with greatest short-term effectiveness was the optimal strategy, at a willingness to pay threshold of £20,000 per QALY gained. In these models the annual probabilities of relapse to smoking, smoking related disease incidence and death have been assumed to be constant [392, 396, 417] compared with the decreases related to time since cessation in the present model. Assuming a sharp fall in

probabilities linked to unfavourable health outcomes, rather than a decline over time, is less realistic, but further biases results towards those with higher effectiveness if the full benefits of smoking cessation are assumed instantly obtainable.

It is difficult to incorporate both an underlying quit rate and transition probabilities that vary with time since quit into a state transition model structure, without incorporating numerous tunnel states. Individual-level models may be a better avenue for accurately quantifying the cost-utility of smoking cessation strategies in future. At least two such models have been built to date [215, 419], and the BIT model described in Chapter 7 takes an individual-level approach which allows accurate and flexible modelling of predicted smoking status post follow-up, as well as incorporation of the link to alcohol use.

The transition probabilities and some parameter inputs presented here were taken from the manufacturer's submission for the NICE varenicline STA [366], and it is not known whether these data are the best currently available. From the results of the deterministic sensitivity analysis, model outputs are robust to changes in parameter inputs apart from the relative effectiveness of the two treatments. Uncertainty around the probabilities of transition to disease states has not been explored, but if the relative risks of smoking-related disease incidence and mortality can be assumed to decrease after smoking cessation, cytisine for smoking cessation will represent a better use of the healthcare budget than varenicline using average values given current information.

6.5. Chapter Summary

This chapter sought to present and analyse results of a standard practice economic appraisal of competing strategies to aid smoking cessation, in order to understand the importance of characteristic and unrealistic modelling assumptions of current practice models. Appraisal of the cost-utility of cytisine versus varenicline to aid smoking cessation, a relevant area of investigation for today's decision makers, has been presented using the BENESCO model structure.

Choosing the optimal smoking cessation strategy is of great consequence for NHS finances, because of the number of current smokers affected. It is correct that this

decision should be based on cost-effectiveness evidence, but it is vital that conclusions from the economic analysis are driven by the relative merits of competing strategies, and not characteristics of the economic model. Model results are highly driven by effectiveness data: because smoking-related diseases are the key driver of both HRQoL and cost differences between comparators, the more effective strategy, which leads to the greatest net non-smoker gain in the cohort, is shown to be the cost-effective comparator. Crucially, the BENESCO model structure assumes no underlying quit rate post trial follow-up. This implicitly exaggerates the relative effectiveness of the most effective strategy considered. Other cohort analyses with differing assumptions and data may have also under-estimated behavioural changes in the medium and long-run [392, 396, 417]. The more recent relapse data employed in this chapter [390] suggested higher relapse than previously estimated [418]. The results of many existing analyses may therefore be driven, at least partly, by unrealistic assumptions about post-trial behaviour.

Results from Chapter 5 suggested that smoking status is both more transient than previous models have assumed and linked to multiple factors, including level of alcohol use. The next chapter describes an individual-level model to appraise competing aids to smoking cessation, which incorporates dynamic projections of extrapolated smoking status based on HILDA data, and incorporates the estimated inter-temporal link to alcohol use, and its consequences. The methods and data to link smoking behaviour to health, HRQoL and costs presented here will be useful model inputs in this individual-level model. This model provides an alternative analytic tool to 'standard practice' models such as the BENESCO model. Analysis using this alternative model in Chapter 8 will explore the extent to which standard practice models of smoking cessation strategies have produced inaccurate results due to unrealistic assumptions and limited data.

7. Chapter 7: The Behavioural Interactions in Tobacco use (BIT) health economic model

7.1. Introduction

The previous chapter demonstrated the methods and results of a cost-effectiveness model typical of existing economic appraisals of smoking cessation interventions. The model made potentially unrealistic assumptions about smoking status post trial follow-up and assumed no link between smoking status and alcohol use.

There are two key objectives of Chapter 7. The first is to describe the methodology of a *de novo* model of the health economic consequences of smoking cessation treatment outcomes, the BIT model. The model accounts for a link between smoking status and alcohol use, using the dynamic equations estimated in Chapter 5. By incorporating these dynamic behavioural equations, the BIT model also improves on standard practice assumptions about smoking status post trial follow-up, by allowing for the influence of age, gender and other important factors on the propensity to smoke. The second is to outline the data and methods to link alcohol use to health in the BIT model.

This chapter is split into two parts, relating to these two objectives. The first part describes the conceptual model, and should help the reader understand the possible pathways of individuals through the model, with reference to a hypothetical smoking cessation treatment patient. Methods to predict future smoking and alcohol use status have been detailed in previous chapters. The second part of this chapter details methods to capture health and cost consequences of alcohol use decisions.

7.2. The Conceptual Model

This narrative first describes the software package within which the BIT model was constructed, then the workings of the model itself.

Simul8, a commercial discrete event simulation (DES) software package, was used to build the model (www.simul8.com). In this application, Simul8 was not employed for its full DES capabilities, but because of its flexible and user-friendly

programming language and interface. Unlike within a typical DES framework, where events occur on a continuous time scale, time is managed through discrete cycles. This framework sits easily with the econometric model outputs from Chapter 5. Nevertheless, there is a clear advantage of using Simul8 software over Microsoft Excel for a relatively complex state-transition cost-effectiveness model such as this. When dealing with diseases with chronic implications, keeping track of patient histories becomes important. In a Microsoft Excel cohort model, this can be achieved by creating health states to differentiate between patients with different histories. The number of health states required for this can quickly become very large though, and difficult to manage. In Simul8, it is relatively easy to assign labels to patients which keep track of their individual history, and then activate logic based on the values within these labels.

As discussed in Chapter 6, this limitation has played an important role in the way economic evaluation models of smoking cessation have been constructed. Models have typically either assumed no future quit attempts after the modelled intervention, as is the case with the BENESCO model, reproduced in Chapter 6, or have assumed constant underlying quit rates and relapse rates after the first year [140, 160, 420]. Evidence from Chapter 5 and Chapter 2 suggests that long-term smoking (and drinking) behaviour is variable and influenced by multiple factors, but modelling would become unmanageable within a Microsoft Excel cohort state-transition model framework if appropriate complexity was to be added. By building this economic model within Simul8, smoking status changes and relapse rates that vary with time since quit and other factors can be applied, marking improvements on existing models. Similarly, incorporating the consequences for alcohol use and alcohol-linked health consequences would have required a number of health states that was considered logistically not possible within a Microsoft Excel cohort state-transition model framework.

Building the model in Simul8 has also had the related advantages of ease of adaptation, transparency through the user interface and Visual Logic code, and relative ease of verification and validation.

For readers unfamiliar with Simul8 and requiring a brief introduction, there are four main components within a Simul8 model, through which work items (e.g. people) travel [421]:

1. Entry Point(s), where work items arrive in the model
2. Queues, where work items wait to be processed by the accompanying Work Centre
3. Work Centres, where work is performed
4. Exit Point(s), where work items leave the model

Information can be stored during a simulation, in the form of spreadsheets, numbers and labels. Labels can be in number form, and are attached to work items as they travel through the simulation, and differ between work items. Numbers and spreadsheets are, by contrast, not work item specific. In a health economic individual-level model such as this, labels are well suited to tracking person-specific attributes such as age, gender and disease presence, whereas numbers can be used to record model outputs, such as total costs, life years and QALYs.

Though it is possible to hold work items within queues and specify a processing time for work centres, when there is no competition for resources within the model, or interaction between work items, it aids model run time to set processing times to zero. Queues are therefore not used in the traditional sense in the model, but used only as an aid for validation and verification. The computational time involved in searching for the next event increases disproportionately with the number of entities within the system.

One simulated individual is followed to death before the next enters the model; processing one entity at a time also aids verification and validation. After model entry, each simulated individual moves between 'work centres', according to transition probabilities that reflect both the label characteristics and current work centre of the individual, with costs and health outcomes updated within each work centre. Discrete time cycles of 1 year are used. To adjust for bias incurred when assuming events occur at the end of each time cycle, a half-cycle correction is applied [422].

Figure 14: Flow diagram describing one person's journey through the model

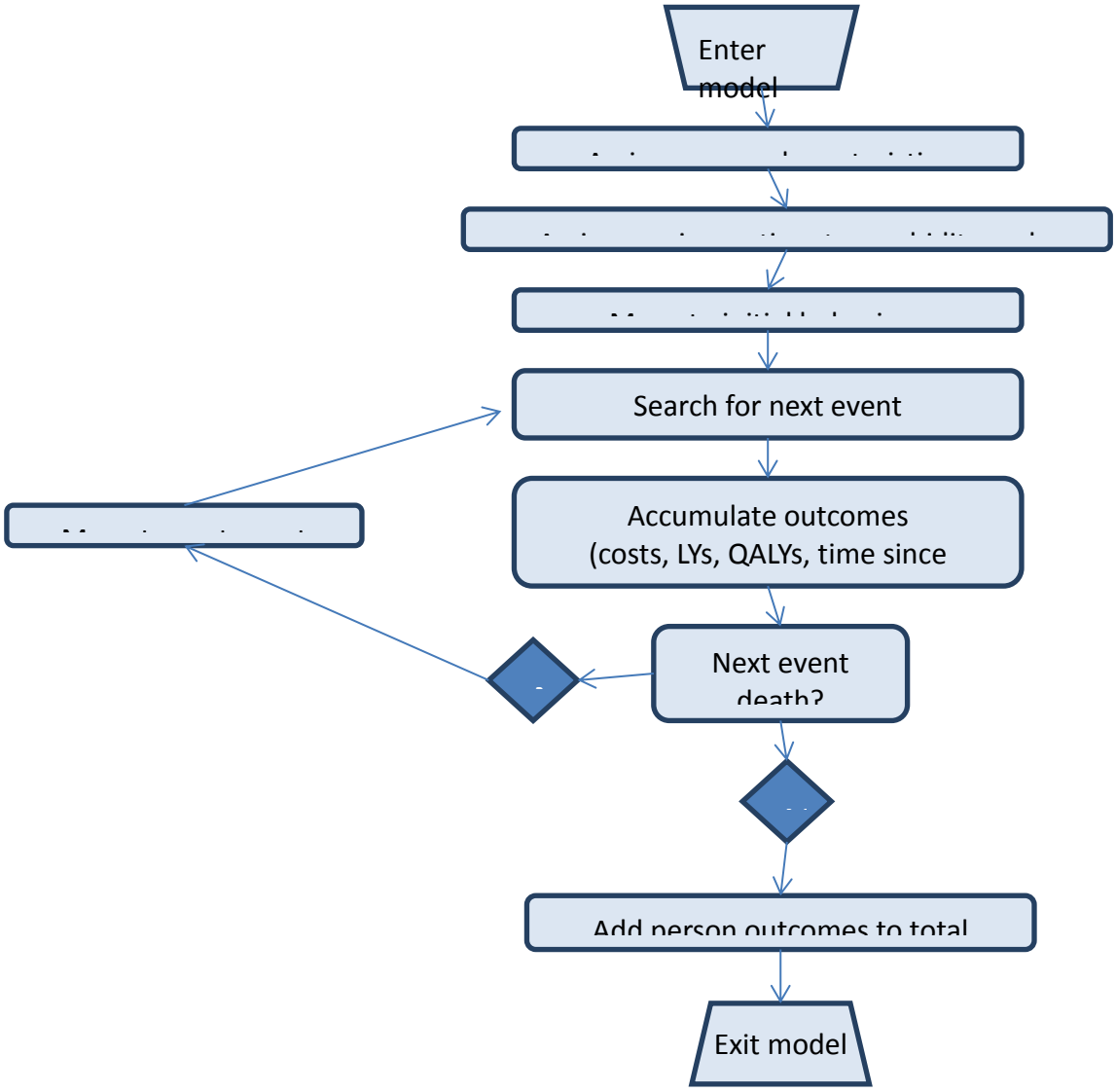


Figure 14 illustrates one simulated person's journey through the model, in simplified terms. Underpinning movement and tracking of characteristics and outcomes for each person, is code written in Simul8's simulation language, Visual Logic (VL). The following narrative seeks to describe the workings of this code, so that the reader can understand the details of the model.

Before a model run

One run of the model generates outcomes of interest (costs, LYs, QALYs) for the sample of interest, for one configuration of parameters sampled given parameter uncertainty.

Before each model run, *reset* logic is called and used to set parameter values to appropriate levels. Because the model can be run as probabilistic or deterministic, *reset* logic sets (i) healthcare costs, (ii) utility and (iii) parameters for the econometric probability equations to values for the current configuration of parameter uncertainty. This is done in two stages. To minimise unnecessary storage of data within Simul8 and to aid verification and validation, N values of parameters tested used in the PSA were sampled a priori in Microsoft Excel. The first stage involves retrieving from Excel the draws of PSA input values associated with the current parameter uncertainty configuration. The second stage involves setting input parameters to these values.

7.2.1. Upon entry

Simulated individuals enter the model at 12 months following smoking cessation intervention. Upon entry, they are assigned age and gender values, in the form of labels. Labels are also used to capture smoking and drinking status. It is assumed that patients do not have any morbidities when entering the model.

Predicted time to death from causes unrelated to alcohol and tobacco (all other cause mortality (AOCM)) is also calculated. Time to AOCM is estimated by comparing age and gender specific risk to a random number draw from the uniform interval [0, 1] each year until the former is the greater, and then stored as a number[9]. This number defines the maximum time to death for each individual; this can be shortened but not extended as individuals move through the model.

The individual then leaves the entry point and moves to one of four **behaviour-related work centres**. These work centres are defined by smoking and drinking status:

- 'NAR, NS' signals not at-risk drinking and non-smoking
- 'NAR, S' signals not at-risk drinking and smoking
- 'AR, NS' signals at-risk drinking and non-smoking
- 'AR, S' signals at-risk drinking and smoking

[9] For brevity, a random draw from the uniform interval [0, 1] is generally referred to as 'random number draw' from here on.

The drinking and smoking labels of the simulated individual leaving the entry point determine to which of these work centres the entity is routed. This was achieved by selecting 'Routing Out' options within the entry point, and routing according to a label, *router*, numerically defined by smoking and drinking status.

To introduce an example simulated individual at this point, assume a 50 year old male, 'Paul', who enters the model as a smoker and at-risk drinker. Paul is routed to the 'AR, S' work centre upon entry.

7.2.2. Behaviour-related work centres

The four behaviour-related work centres are broadly similar, so describing Paul's movement through the 'AR, S' work centre highlights the mechanics of the other three.

The aims of the code within behaviour-related work centres are to (i) determine which event occurs next and route accordingly, (ii) record costs and health outcomes incurred whilst in the work centre and (iii) update person-specific label values.

7.2.2.1. (i) Determining the next event and routing

There are eight possible next events Paul could experience after leaving 'AR, S', and *router* is updated accordingly throughout the work station VL. Box 1 details the router values attached to each possible next event.

Box 1: Next events for behaviour-related work centres

router = 1	Next event: Change in drinking status
router = 2	Next event: Death
router = 3	Next event: 'Hospital' (incidence of smoking or drinking related morbidity)
router = 4	Next event: Change in smoking status
router = 5	Next event: Simultaneous change in drinking and smoking status
router = 6	Next event: Change in drinking status and 'Hospital'
router = 7	Next event: Change in smoking status and 'Hospital'
router = 8	Next event: Simultaneous change in drinking and smoking status & 'Hospital'

First, the VL code calculates the predicted time to a change in drinking status. This is done using outputs from the econometric model described in Chapter 5. Whether Paul changes his drinking status next year is determined by: current drinking status; current smoking status; gender; age in a year's time; unobserved time-variant and time-invariant factors that influence the propensity to drink to at-risk levels; and the remaining independent variables in the econometric at-risk drinking equation. Paul is currently an at-risk drinker. The output from the at-risk drinking equation is the latent propensity for at-risk drinking; as described in Chapter 5, if this is less than zero, Paul is predicted to change his drinking behaviour to not at-risk next year. If this is the case, Paul's *time to drinking status change* is set to 1. If not, the process is repeated with age and price variables appropriately adjusted until either drinking status change is predicted or age reaches 100 years, whereby *time to drinking status change* is recorded.

Assuming a change in drinking status is at present the next event, Paul's *router* label is set to 1, and a number recording *time to behaviour change* is set to *time to drinking status change*, before time to a change in smoking status is calculated. The method for this is equivalent to calculating time to drink status change, but using the smoking equation estimated in Chapter 5. If time to smoking status change is less than time to drinking status change, the next event is now behaviour change to non-smoking, *time to behaviour change* is updated and *router* is set to 4. If both behaviours are calculated to change in the same year, *router* is set to 5.

Next, a number representing *time to death* is estimated. There are three broad categories of death that Paul is at-risk of every year: alcohol-related disease (ARD) mortality; smoking-related disease (SRD) mortality; and AOCM. Outstanding risk estimations are detailed in section 7.3.2. Time to AOCM is the number calculated upon entry, less any time spent in the model; *time to death* is first set to this number. Time to ARD mortality is estimated by comparing age- and gender-specific risk to a random draw each year until the former is the greater for each alcohol-related disease or injury in the model. If time to ARD death is less than time to AOCM, the number tracking *time to death* is updated. Time to SRD mortality is estimated in a similar fashion only if Paul has one of the four chronic SRDs with associated mortality in the smoking model: COPD, lung cancer, previous CHD or previous stroke. Again, if time to SRD death is less than present *time to death*, the *time to death* number is updated.

The number *time to death* is then compared to *time to behaviour change*, to see if behaviour change occurs first. Importantly, the code prioritises certain events over others, if they occur at the same time. Events are prioritised in order of severity, so if death and behaviour change are estimated to occur simultaneously, death takes priority. If *time to death* is lower or equal to before *time to behaviour change,* the label *router* is set to 2. A new number, *time to next event*, is set to whichever event occurs soonest.

Third, the VL code estimates time to morbidity. There are two broad types of morbidity Paul can incur: ARD morbidity and SRD morbidity. Using familiar comparisons of risk estimates to random number draws, time until morbidity is

estimated for each ARD in turn, and a new number, *time to hospitalisation,* is set to store the lowest time to morbidity. The term hospitalisation is used loosely to capture incidence of all morbidity, though SRD incidence data is not based solely on hospital records. Time and cause of morbidity are recorded here, using numbers such as *time of liver cancer*. This is important, as if hospitalisation occurs next these numbers are used to assign labels for chronic disease within hospital VL, as explained later. Time until SRD morbidity is then estimated for COPD, lung cancer, CHD, stroke and asthma using risk data from the smoking model in Chapter 6. The number *time to hospitalisation* is updated if SRD morbidity is estimated to occur before ARD morbidity.

If death is the next event, the VL code then compares *time to death* to *time to hospitalisation*, to see which occurs first. If it is the latter, *time to next event* is set to *time to hospitalisation*, and *router* is set to 3. If both are equal, death takes priority over morbidity and behaviour change, as a matter of severity.

If however, behaviour change is estimated to occur before death, the VL code instead compares *time to behaviour change* to *time to hospitalisation*. If the latter occurs first, *time to next event* is set to *time to hospitalisation*, and *router* is set to 3. If both are equal, and drinking status change occurs before smoking status change, router is set to 6. If both are equal, and smoking status change occurs before drinking status change, router is set to 7. If both are equal, and both drinking and smoking status changes occur simultaneously, router is set to 8.

In the smoking model in Chapter 6, risks of SRDs are lower for long-run smoking quitters than short-run quitters; this complexity is incorporated into the BIT model using VL. The label 'quit years' is updated upon work centre exit. As Paul is currently a smoker, his 'quit years' label is set to 0. If Paul was in a non-smoking work centre, his annual risk of death and mortality would reduce after 4 years of predictions of no event, by means of the number 'count quit years', based on the label 'quit years' and updated with annual estimations of time to event within non-smoking work centre VL.

7.2.2.2. (ii) Recording costs and health outcomes

The only costs incurred within behaviour-related work centres are annual costs from chronic SRDs. If one or more chronic SRD is present (as recorded by a label), the cost is calculated as the years spent in the work centre multiplied by the annual cost. The discounted cost is calculated by discounting the years spent in the work centre before multiplication by the estimated annual cost. This is done by calculating the integral of the exponential survival curve, between work centre entry and exit. The formula for this calculation is as follows:

$$Discounted\ years = \frac{e^{(-DRi * TONE)}}{-DRi} - \frac{e^{(-DRi * TOLE)}}{-DRi} \quad (41)$$

$$DRi = \ln(1 + DR)$$

Where DR is the annual discount rate, DRi is the instantaneous discount rate, $TONE$ is *time of next event,* measured in years, calculated in Paul's instance as the difference between *time to next event* and model entry, and $TOLE$ is *time of last event*, which in Paul's case was time at model entry, zero. $TOLE$ is set equal to the number of years the entity has been in the model immediately prior to recording of health and cost outcomes. The costs and discounted costs incurred are then added to the running *Total Costs* number.

Simulated individuals like Paul are continually accumulating life years as they move through the model. These are calculated as above, and added to *Total LYs* and *Total Discounted Costs*, as appropriate. To calculate the QALYs Paul has accrued in the 'AR, S' work centre, the age and gender specific general population utility value is adjusted for any chronic ARDs or SRDs present, and multiplied by life years spent in the work centre. Discounted QALYs are calculated as discounted work centre LYs multiplied by utility, and *Total QALYs* and *Total Discounted QALYs* are updated accordingly.

Finally, a new number, *years in model*, is set equal to *TONE*.

7.2.2.3. (iii) Updating person-specific label values

Lastly, the labels *smoker* and *at-risk drinker* are updated according to the next event, using the label *router*. Let us assume that, unfortunately for Paul, his next event is lung cancer at age 60. The labels *smoker* and *at-risk drinker* remain at

values of 1, and router is set to 3, and Paul travels to the workstation 'Hospital AR, S'.

7.2.3. Hospital work centres

As with behaviour-related work centres, the four hospital work centres are broadly similar and describing the mechanics of one should be sufficient to convey the workings of the other three.

The aims of the code within hospital work centres are equivalent to the aims listed for behaviour-related work centres: (i) determine which event occurs next and route accordingly, (ii) record costs and health outcomes incurred between events and (iii) update person-specific label values. However, there are key characteristics of hospital work centres that mean the code used to achieve each aim requires further description.

7.2.3.1. (i) Determining the next event, routing and assigning labels

The primary difference between behaviour-related and hospital work centres is that simulated individuals stay in hospital work centres for, at most, one year. Hospital work centres are needed to capture the cost and utility implications of morbidity incidence; after one year, labels can be updated to capture any chronic disease cost and utility implications for subsequent work centres.

As Paul enters the 'Hospital AR, S' work centre, he is faced with nine possible next events, assigned to the *router* label as detailed in Box 2.

Box 2: Next events for hospital work centres

router = 1	Next event: Change in drinking status
router = 2	Next event: Death
router = 3	Next event: 'Hospital' (again)
router = 4	Next event: Change in smoking status
router = 5	Next event: Simultaneous change in drinking and smoking status
router = 6	Next event: Previous smoking and drinking status
router = 7	Next event: Change in drinking status & 'Hospital'
router = 8	Next event: Change in smoking status & 'Hospital'
router = 9	Next event: Simultaneous change in drinking and smoking status & 'Hospital'

The default next event following a hospital work centre is the previous behaviour-related work centre; if Paul does not die, return to hospital or change his behaviour in the year after morbidity, he returns to 'AR,S'. At the start of the VL code, *router* is set to 6.

As in behaviour-related work centres, death takes priority over hospitalisation and behaviour change, when these events are predicted to occur at the same time. The code estimates risk of death next. Instead of estimating *time to death*, the task in hospital work centres is to predict whether death occurs in the next year.

For Paul, this means comparison of annual death risk with a random number draw, for SRDs, ARDs and AOCM, according to his age, gender and chronic disease status. There is also a potentially heightened risk of death for 90 days in hospital work centres, if hospitalisation was for an alcohol-related condition. The rationale behind this is explained in the description of alcohol behaviour risks in the second part of this chapter. Though Paul's morbidity was not alcohol-related,

unfortunately he was predicted to die as a result of heightened mortality risk in the year following lung cancer incidence.

If 90 day death had been predicted, *router* would have been set to 2 and *time to next event* to 90 days. As one year mortality was predicted, *router* is set to 2 and *time to next event* to 1 year. In fact, without a prediction of death, the number *time to next event* could at this point confidently be set to 1 year.

If death had not been predicted to occur in the next year, whether drinking and smoking status changes in the next year would be estimated, comparing predicted probabilities to random number draws. If a change in drinking status is predicted, *router* is set to 1 and *at-risk drinker* is set to 0. If a change to smoking status is predicted, *router* is set to 4 and *smoker* is set to 0, unless drinking status change is also predicted, in which case *router* is set to 5 and *at-risk drinker* is also set to 0.

Next, costs and health outcomes accumulated within the workstation are calculated. The costs and utility adjustments incurred through morbidity are attributed using numbers recording times of hospitalisation for each model disease, as will be described next. The VL code predicting rehospitalisation updates numbers tracking *times to* and *of* hospitalisation by cause, and so must be run after costs and health outcomes have been recorded.

If the next event was not death, hospitalisation code would compare risk for one year with a random number draw, for all smoking- and alcohol-related diseases. Numbers recording times to hospitalisation and time of condition-specific morbidity are reset and updated. If neither death nor a change in behaviour have been predicted in the next year (*router* is currently set to 6), but rehospitalisation is predicted, *router* would be set to 3 and, because behavioural labels were potentially changed in this work centre when risk of behaviour change was assessed, *at-risk drinker* and *smoker* labels would be reset to 1, in Paul's case. If a change in drinking status was predicted (*router* is currently set to 1) and rehospitalisation was to be also predicted, router would be set to 7 and *at-risk drinker* and *smoker* labels to 0 and 1, respectively. If a change in smoking status was predicted (*router* is currently set to 4) and rehospitalisation was to be also predicted, router would be set to 8 and *at-risk drinker* and *smoker* labels to 1 and 0,

respectively. If a simultaneous change in drinking and smoking status was predicted (*router* is currently set to 5) and rehospitalisation was to be also predicted, router would be set to 9 and *at-risk drinker* and *smoker* labels to 0 and 0, respectively.

7.2.3.2. (ii) Recording costs and health outcomes and assigning more labels

Following prediction of behaviour status change, work centre costs are calculated. The costs incurred by a trip to hospital are dependent on the reason for the hospital visit. In the previous work centre, whether it was behaviour-related or a hospital work centre, numbers recording time of morbidity for each disease and a number tracking *time of hospitalisation* were calculated. It is therefore possible to determine the morbidity cause, by checking if *time of hospitalisation* is equal to time of morbidity for each SRD and ARD. If so, a disease specific label can be set to 1 to track presence of this disease in future, and any disease-specific hospitalisation costs can be added to *Total Costs*. It is important to note that this code allows hospitalisation for more than one condition at one time. Paul is here attributed a label for lung cancer, and cost for one year of care with the disease.

To record health outcomes, first the age and gender specific general population utility value is adjusted for any chronic ARDs or SRDs present, as in behaviour-related work centres. For Paul, the general population utility for a 60 year old male is multiplied by the utility level associated with lung cancer. This utility value would have been multiplied by 90/365 if 90 day death had occurred, but is multiplied by 1 otherwise, to calculate work centre QALYs. Work centre life years are either 90/365 or 1. Then, utility decrements are applied: (i) for two weeks upon entry to the hospitalisation work centre, when utility is set to 0 (though SRD data are not based on hospital admissions, a sharp temporary fall in utility is assumed when learning of a chronic SRD) and (ii) for eight subsequent weeks if the reason for hospital admission was acute. These values can be added to *Total QALYs* and *Total LYs* numbers.

Annual costs, life years and QALYs are discounted using equation (41), as are temporary post-hospital acute condition decrements. One-off costs of hospitalisation and the two week hospitalisation utility decrement are discounted using the following formulae, where *DR* is the annual discount rate, and added to

Total Discounted Costs, *Total Discounted QALYs* and *Total Discounted LYs*, respectively:

$$Discounted\ costs = \frac{costs}{DR^{Years\ In\ model}}$$

$$Discounted\ QALYs = \frac{QALYs}{DR^{Years\ In\ model}}$$

$$Discounted\ LYs = \frac{LYs}{DR^{Years\ In\ model}}$$

After work centre outcomes have been recorded and rehospitalisation risk accounted for, the variable Years in Model can be set equal to TONE, in anticipation of the next event. Unfortunately for Paul, his next event is death and he leaves the model.

7.2.4. After exit and on end run

As Paul meets the model end point, the next simulated individual enters the model. This individual is assigned age, gender and behaviour status, and then travels through the model experiencing events according to risk and chance, accumulating costs and health outcomes simulating real life, like Paul before them.

When the entire cohort of simulated individuals have travelled through the model, *End Run* logic enables per patient outcomes to be calculated, and if PSA is being run, the model is set to run again using the next sample from parameter uncertainty. *Reset* logic, described at the outset, then starts the process again.

7.2.5. Limitations

Despite the flexibility of Simul8 as a modelling platform, there are some limitations to this conceptual model. Firstly, time is modelled as discrete. This is for practical reasons: it sits easily with much of the input data including the dynamic behaviour equations. Though a divergence from reality, it is not expected that the treatment of time as discrete will bias any analyses using the model in favour of any particular treatment.

Secondly, the model does not capture health and costs for the first year after treatment for smoking cessation. This is for transparency and efficiency: it enables one full run of the model to be analysed posthumously for multiple treatment

strategies. Again, it is not anticipated this limitation will bias any analysis using the model.

Thirdly, the model assumes no interactions between individuals. For example, if two people die in the same car crash that resulted from drink driving, the model cannot account for this. Incorporating such detail into the model, and thus assessing the consequences, would require further work, the feasibility of which has been assessed in a recently completed doctoral thesis [423].

Fourth, the model structure does not explicitly incorporate aided smoking cessation attempts after model entry. The influence of smoking cessation aids upon projections of behaviour is implicitly incorporated by the dynamic behavioural equations estimated in Chapter 5, as these were generated using data from the Australian public collected in the 21st Century, when pharmaceutical aids to smoking cessation were available, mirroring the situation in the UK. It is possible that explicit incorporation of smoking cessation attempts would influence economic appraisal results. Consider an appraisal of two competing treatments for smoking cessation, where treatment A is more costly and more effective than treatment B. If adopting a treatment means said treatment is used in all future cases when a smoker requires treatment to assist a quit attempt, and smokers make multiple quit attempts, all future treatment costs and effectiveness rates will be higher for treatment A than treatment B. It is unclear whether not explicitly accounting for the costs and effects of subsequent quit attempts would favour treatment A or treatment B in this example, but in an appraisal of cytisine versus varenicline, the superiority of cytisine may be understated.

There are several issues with explicitly and accurately incorporating the costs and consequences of future cessation attempts into the model, however. Firstly, it would be difficult to reconcile implicit and explicit incorporation of future quit attempts. Secondly, adoption of one treatment would not mean that treatment would be used in all future quit attempts for unsuccessful quitters. An unsuccessful quit attempt with one treatment may actually make another treatment more likely in a subsequent attempt [424]. Information would be needed as to the probability of quit attempts across time and the probability of each

available aid being used in future attempts. The STOP model study identified in Chapter 3 [214] generated estimates for these two parameters using a cross-sectional survey of US college students (n=1078) [216]. Aside from the limitations of these data in applicability to a contemporary appraisal of competing smoking cessation aids, crucially, the survey does not contain data on the use of cytisine. Further, knowledge would be required about the effectiveness of subsequent treatment using each strategy in individuals who had previously relapsed using that treatment.

7.2.6. Summary of the conceptual BIT model description

This narrative has hopefully proved useful to the reader in explaining the conceptual mechanics of the BIT model, through both a brief account of the software platform Simul8, and the travails of our hypothetical hero, Paul, as well as setting out limitations of the modelling approach. The next chapter re-analyses the competing cost-effectiveness of cytisine and varenicline for smoking cessation, using the BIT model. However, while much of the data to populate the BIT model has been described in previous chapters, the methodology and data to quantify health and cost consequences of different levels of alcohol use is yet to be explained. The second part of this chapter now details the data used to link alcohol use to health and health-related costs in the BIT model.

7.3. Quantifying risks and outcomes associated with alcohol behaviour

This subsection explains the derivation of BIT model inputs yet to be accounted for. Namely, these are alcohol-related condition morbidity and mortality risks, and risks of death from causes unrelated to alcohol or tobacco use. This is achieved in three main parts. Firstly, the conceptual pathway of alcohol-related health risks is described. Secondly, the methods used to estimate these risks are explained. Thirdly, the method to quantify cost and utility effects related to alcohol consumption are set out. With the aim of this subsection achieved, the limitations of these methods to link alcohol use to health are discussed.

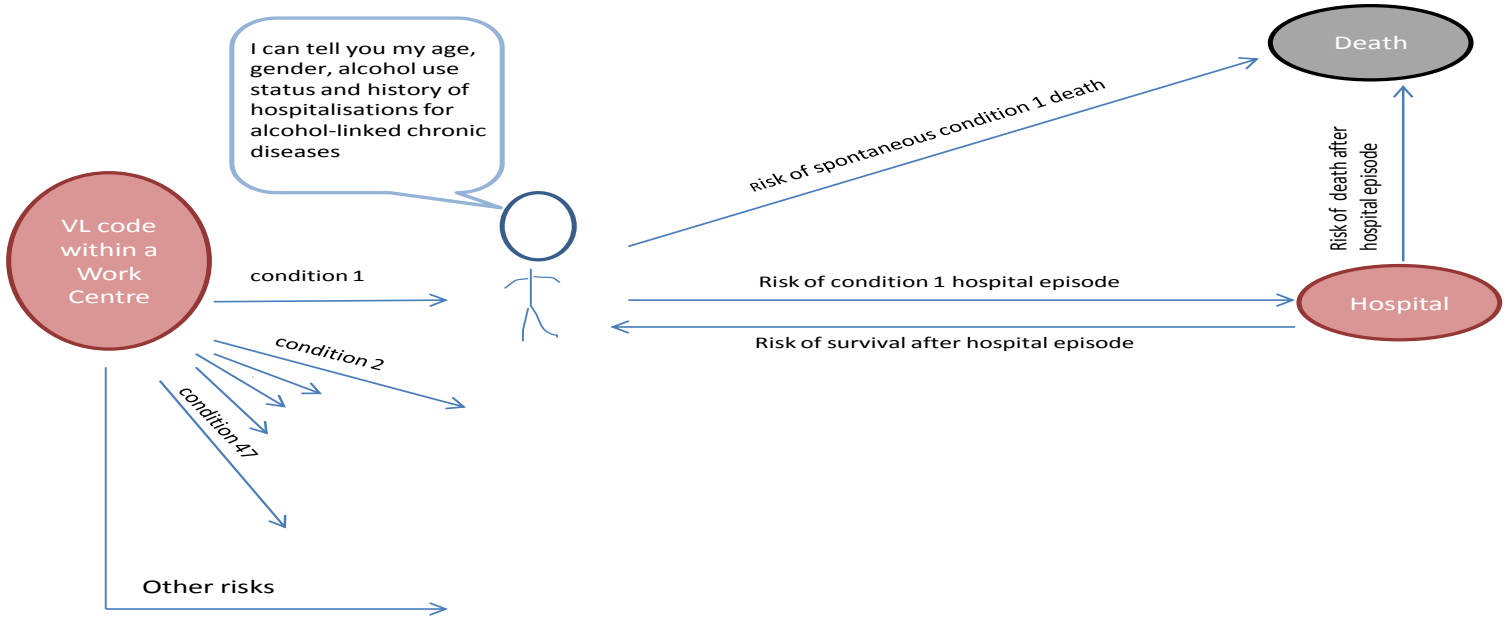
7.3.1. The conceptual care pathway of alcohol-related health risks

In order to set out how risks of alcohol-related mortality and morbidity are captured in the BIT model, it is useful to describe the various alcohol-related

health risks faced by simulated individuals. Figure 15 shows a snapshot of these risks and how simulated individuals in the BIT model encounter them. This figure intentionally highlights the part of the BIT model under current consideration, while ignoring other elements of conceptual pathway for simulated individuals, such as competing risks of behaviour change, smoking-related health effects and AOCM.

Based on their drinking, age and gender characteristics, each year an individual is in any of the work centres in the BIT model, they have a risk of spontaneously dying from an alcohol-related condition, and a risk of hospitalisation. If an individual is hospitalised with a condition, they then have a heightened risk of dying from that condition for a short period afterwards. If they survive, the next year their hospitalisation and death risks will be again determined by their drinking, age and gender characteristics.

Figure 15: The conceptual care pathway of alcohol-related health risks



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There are forty-seven alcohol-related conditions in the model, as described below. So as well as risks for condition 1, the boastful and faceless individual in Figure 15 faces risks for forty-six other alcohol-linked conditions, as well as the risk of dying from a non-alcohol-related cause.

With reference to Figure 15, it is apparent that three types of risk estimates are needed for each alcohol-related condition in the model, in addition to the risk of death from other causes, with sensitivity to alcohol use status, age and gender:

1. Risk of hospital admission for each condition
2. Risk of death following hospital admission for each condition
3. Risk of 'spontaneous' death for each condition

Estimation of risk types 1, 2 and 3 is described next, with continued reference to alcohol-linked conditions in the model, to aid clarity.

7.3.2. Estimating risks for death and hospitalisation

Accurately estimating the risks identified in Figure 15 is an extremely challenging task, for a number of reasons. The range of health-related events and diseases that can be partially or wholly linked to alcohol use is wide, and because of data paucity, uncertain. Linking alcohol consumption patterns to risk of morbidity and mortality is also highly difficult, not least because of confounding factors and variability in risks across individuals. Further, as discussed in Chapter 2 and 5, data on alcohol consumption is in short supply and potentially subject to widespread under-reporting.

Much of the methods and data to estimate risks for death and hospitalisation used in the BIT model are adapted from previous studies with these aims [253, 265] and are presented here for clarity and completeness. The first step in estimating risks for the model is identifying the conditions that are causally linked to alcohol consumption. The forty-seven conditions defined as fully or partially attributable to alcohol in the SAPM [253], as identified in an earlier report from the North West Public Health Observatory (NWPHO) [265], are used here. These conditions can be sub-divided as acute or chronic, in terms of their implications for future health, and fully or partially attributable to alcohol, and are listed in Table 22. This is the

most extensive battery of alcohol-related conditions used in a known economic model to date, and exceeds that of previous work [225, 226, 229, 232, 235, 238, 243, 246, 249-252, 254, 255, 257, 259, 425].

Table 22: Conditions Included in Mortality and Morbidity Calculations[10]

Condition	ICD-10 code(s)	Source of Alcohol Attributable Fraction or Relative Risk Function
Road traffic accidents	V (many)	Ridolfo *et al* 2001 [426]
Pedestrian traffic accidents	V (many)	
Water transport accidents	V90-V94	Single *et al* 1996 [427]
Air and space transport accidents	V95-V97	English *et al* 1995 [428]
Falls	W00-W19	Ridolfo *et al* 2001 [426]
Work/machine injuries	W24-W31	English *et al* 1995 [428]
Firearm injuries	W32-W34	Single *et al* 1996 [427]
Drowning	W65-W74	English *et al* 1995 [428]
Inhalation of gastric contents	W78-W79	Single *et al* 1996 [427]
Fire injuries	X00-X09	
Accidental excessive cold	X31	
Intentional self-harm/Event of undetermined intent	X60-X84,Y10-Y34	English *et al* 1995 [428]
Assault	X85-Y09	Single *et al* 1996 [427]
Lip, oral and pharyngeal cancer	C00-C14	Tramacere *et al* 2010 [429]
Oesophageal cancer	C15	Corrao *et al* 2004 [430]
Malignant neoplasm of colon	C18	
Malignant neoplasm of rectum	C20	
Liver cancer	C22	
Malignant neoplasm of larynx	C32	Islami *et al* 2010 [431]
Breast cancer	C50	Key *et al* 2006 [432]
Epilepsy and status epilepticus	G40-G41	Samokhvalov *et al* 2010 [433]
Hypertensive diseases	I10-I15	Corrao *et al* 2004 [430]
Cardiac arrhythmias	I47-I48	Kodama *et al* 2011[434]
Haemorrhagic Stroke	I60-I62, I69.0-I69.2	Corrao *et al* 2004 [430]
Ischemic Stroke	I63-I66, I69.3-I69.4	
Oesophageal varices	I85	
Gastro-oesophageal laceration-	K22.6	Purshouse *et al* 2009

[10] Table adapted from Purshouse *et al*, 2009 253. Purshouse R, Brennan A, Latimer N, Yang M, Rafia R. Modelling to assess the effectiveness and cost-effectiveness of public health related strategies and interventions to reduce alcohol attributable harm in England using the Sheffield Alcohol Policy Model version 2.0. Sheffield, UK: School of Health and Related Research (ScHARR), University of Sheffield; 2009.

Condition	ICD-10 code(s)	Source of Alcohol Attributable Fraction or Relative Risk Function
haemorrhage syndrome		[253]
Unspecified liver disease	K73, K74	Corrao *et al* 2004 [430]
Acute and chronic pancreatitis	K85,K86.1	
	L40 excluding	
Psoriasis	L40.5	Gutjahr *et al* 2001 [435]
Spontaneous abortion	O03	
Diabetes mellitus	E11	
Ischemic heart disease	I20-I25	Corrao *et al* 2004 [430]
Cholelithiasis	K80	Gutjahr *et al* 2001 [435]
Mental and behavioural disorders due to alcohol	F10	100% Attributable
Ethanol poisoning	T51.0	
Methanol poisoning	T51.1	
Toxic effect of alcohol, unspecified	T51.9	
Accidental poisoning by and exposure to alcohol	X45	
Alcohol-induced pseudo-Cushing's syndrome	E24.4	100% Attributable
Degeneration of nervous system due to alcohol	G31.2	
Alcoholic polyneuropathy	G62.1	
Alcoholic myopathy	G72.1	
Alcoholic cardiomyopathy	I42.6	
Alcoholic gastritis	K29.2	
Alcoholic Liver Disease	K70	
Chronic pancreatitis (alcohol-induced)	K86.0	

7.3.2.1. Conditions partially attributable to alcohol

For over ten years, researchers from around the world have been attempting to link mortality and morbidity risks to alcohol use in the context of these challenges, with an impetus for research emanating from the World Health Organization (WHO) [436, 437]. The method that has become prevalent for events and diseases (collectively termed 'conditions' in this thesis) *partially* attributable to alcohol involves the use of '*alcohol-attributable fractions*' (AAFs). An AAF can be defined as the proportion of condition risk that would have been absent without exposure to alcohol [265].

The AAF of a condition is intrinsically linked to the relative risk (RR) of experiencing that condition at different levels of alcohol use. Equation (42) describes this relationship [265]:

$$AAF = \frac{\sum_{i=1}^{I} p_i(RR_i - 1)}{\sum_{i=0}^{I} p_i(RR_i - 1) + 1} \quad (42)$$

Here, i (0 to I) are alcohol consumption categories, RR_i is consumption group-specific relative risk of mortality (exposed versus unexposed groups), p_i is the proportion of the population in the *i*th consumption category. If a parameterised RR equation is available linking consumption to harm for a condition, it is possible to derive a condition AAF estimate. Equally, it is possible to estimate parameters for an RR function with a given functional form, from an AAF estimate.

With knowledge of an AAF and corresponding RR function for each condition, it was possible to estimate the key risks for the model identified above, with access to population figures and data on numbers of hospital admissions and deaths by condition. Annual numbers of deaths and person specific hospital admissions for the 47 conditions in Table 22 were taken directly from the NWPHO report [265], derived by the authors from ONS mortality statistics and HES hospital admissions data, respectively. These data, shown in Table 51 and Table 52 of Appendix E, are from 2005/2006 and are somewhat dated, but were the most appropriate for a combination of reasons. First, given time restraints, alcohol use data for England were only available for this time period, and to link alcohol use to health outcomes it was important that data from aligning time periods were used. Second, the data are specific to gender and age categories across which risks for alcohol-linked diseases vary, and importantly, patient-specific [253, 265]. This level of detail in hospital admissions data could only otherwise be acquired in raw form with an Extract Services Request, and was considered beyond time resource constraints.

To describe the process of generating risk inputs for the model, calculations of risks for males aged 75 and over for the model condition lip, oral and pharyngeal

cancer are shown. First, the annual risk of hospital admission was calculated, using the following equation:

$$hospitalisation\ risk = \left[\frac{(number\ of\ hospitalisations)\times(1-AAF)}{population}\right] \times RR_{alcohol\ use\ status} \quad (43)$$

For now, let us work with figures of 0.40 for the AAF and 2.65 for the relative risk for this group; the rationale of these numbers will become clear in this section. ONS population data estimated 1,477,700 men in this age group [438] (Table 53, Appendix E) and Table 51 shows 703 condition-specific hospitalisations. The risk of hospitalisation for lip, oral and pharyngeal cancer for males aged 75 and over that drink to at-risk levels was therefore:

$$\left[\frac{(703)x(1-0.40)}{1{,}477{,}700}\right] \times 2.65 = 0.00076\ (2sf)$$

Next, the elevated risk of death following hospitalisation for each condition was calculated, based on Hospital Episode Statistics (HES)-ONS linked data which captures deaths of people who have been admitted to hospital, up to 90 days after a hospital admission, by primary diagnosis upon hospital admission and primary cause of death [439]:

$$death\ risk\ after\ hospitalisation = \frac{number\ of\ deaths\ at\ 90\ days\ after\ admission}{number\ of\ admissions} \quad (44)$$

Limitations of the HES-ONS linked data were the lack of age- or gender-specificity, or information on differences in mortality for disease categories within ICD-10 codes. To overcome these problems, (i) HES-ONS data were distributed across model sex and age categories according to the distribution of morbidity and mortality observed in the NWPHO report; (ii) condition-specific mortality was assumed consistent within ICD-10 codes. The HES-ONS linked data were also not patient-specific, with the likely implication that the person-specific ninety-day death rate was under-estimated.

To illustrate this method, for lip, oral and pharyngeal cancer, the HES-ONS data showed 1,872 ninety day deaths linked to 19,672 admissions (Table 57, Appendix E). The NWPHO report recorded 16.87% of deaths and 11.99% of hospital

episodes for lip, oral and pharyngeal cancer to be attributable to males aged 75 and over. The death risk after hospitalisation was therefore calculated as follows:

$$\frac{(1872) \times (0.1687)}{(19672) \times (0.1199)} = 0.1339\ (4dp)$$

HES-ONS linked data were not available for the partially-attributable acute conditions in Table 22, or accidental poisoning by exposure to alcohol. For these conditions, defined within ICD-10 documentation as *external causes of morbidity and mortality* [440], data from a recent study of the epidemiology of trauma deaths in the UK study was utilised [441]. This study used Trauma Audit and Research Network (TARN) Database statistics collected between 2000 and 2010, and found 43,958 trauma admissions linked to 6,867 deaths in acute care within 93 days. Limitations of these data included absence of age- or gender-specificity, and information on differences in mortality for disease categories within and between ICD-10 codes. Using a similar approach as for other conditions in the model, the trauma data were distributed across model sex and age categories according to the distribution of morbidity and mortality observed in the NWPHO report and condition-specific mortality was assumed consistent across *external causes of morbidity and mortality*.

For some conditions, the death risk after hospitalisation predicted by ONS-HES linked or TARN data implied more deaths than recorded in Table 52. This was explicable for many cases, given the limitations of the ONS-HES and TARN data for this purpose. In these cases, the death risk following hospitalisation was estimated as the number of age, gender and disease specific deaths in Table 52, divided by the corresponding number of person-specific hospital admissions in Table 51.

The risk of spontaneous death for each condition can now be calculated. First, the estimated annual number of spontaneous deaths is calculated:

$$number\ of\ spontaneous\ deaths\ = \\ total\ deaths - (number\ of\ hospitalisations) \times (death\ risk\ after\ hospitalisation) \quad (45)$$

For our elderly males, the recorded total deaths in a year for lip, oral and pharyngeal cancer is 254 (Table 52), the number of condition-specific hospitalisations is 703 (Table 51) and the risk of condition-specific hospital death has been calculated as 0.1339. The estimated annual number of spontaneous deaths caused by lip, oral and pharyngeal cancer is therefore calculated as just under 160:

$$254 - 703 \times 0.1339 = 159.88\ (2dp)$$

Finally, the annual risk of spontaneous death, differing by alcohol use status, can be estimated using population data and knowledge of relative risks:

$$risk\ of\ spontaneous\ death = \left[\frac{(number\ of\ spontaneous\ deaths) \times (1 - AAF)}{population}\right] \times RR_{alcohol\ use\ status} \quad (46)$$

Again, let us work with figures of 0.40 for the AAF and 2.65 for the relative risk for lip, oral and pharyngeal cancer among men aged 75 and over. Recalling the population figure of 1,477,700 for this group, the following annual risk of dying from lip, oral and pharyngeal cancer, when they haven't been hospitalised for the condition in the past year is calculated:

$$\left[\frac{(159.88) \times (1 - 0.40)}{1{,}477{,}700}\right] \times 2.65 = 0.00017\ (2sf)$$

The remaining health risk faced by simulated individuals is that of dying from causes that aren't linked to alcohol, or smoking. Risks of other cause mortality are calculated, by age and gender, from the ONS population and mortality statistics, as follows:

$$risk\ of\ other\ cause\ death = \frac{deaths - alcohol\ deaths - smoking\ deaths}{population} \quad (47)$$

Where the number of alcohol deaths is the total number of deaths attributed to the 47 alcohol-linked conditions in Table 52 and the number of additional smoking deaths is the total number of deaths attributed to lung cancer and COPD, the two mortality-linked smoking related diseases in the model which are not also captured in Table 22, in ONS death by cause data for the corresponding time period [442].

Equations (43) to (46), (47), the accompanying text and worked example have explained the derivation of the hospitalisation and death risks for the thirty-four conditions in the model partially attributable to alcohol. The devil is in the detail, though, and derivation of RR functions and AAFs for each of these conditions now warrants explanation.

Generating and using RR functions and AAFs

The existing literature was of use in linking alcohol consumption patterns to risk of morbidity and mortality. Leading work in this area has been in the form of meta-analyses of epidemiological studies (case-control or cohort) focusing largely on partially-attributable conditions with chronic implications [429-435]. Functions linking average daily alcohol intake to risk have been estimated in these meta-analyses using random effects models, as reported in Table 50 of Appendix E. Typically, these functions are linear, or linear on a logarithmic scale, with the exception of diseases more strongly linked to alcohol (various neoplastic conditions including liver cancer, as well as oesophageal varices and liver disease and cirrhosis) where risk flattens out at higher doses, and diseases where there is thought to be a J shaped relationship between consumption and harm (ischaemic heart disease, diabetes mellitus, cholelithiasis) [430, 431, 435].

Using the distribution of alcohol consumption reported above and the published risk functions in Table 50, it was possible to derive AAFs for partially-attributable chronic conditions using the relationship described in equation (42). To illustrate this process, let us refer again to the familiar example of lip, oral and pharyngeal cancer, and explain in turn the RR figure of 2.65 and AAF of 0.40 used in the above calculations of disease mortality. A meta-analysis of alcohol drinking and oral and pharyngeal cancer provided the following function linking average daily grams of alcohol consumption (x) to disease risk [429]:

$$\ln(RR) = 0.02572x - 0.00006x^2 \tag{48}$$

The AAF for lip, oral and pharyngeal cancer was then calculated using this equation and the estimated distribution of alcohol use in the sub-population at

hand, using the relationship between relative risk and the alcohol-attributable fraction, described in equation (42).

The profile of alcohol use used in estimation of mortality and morbidity risks is based on GHS 2006 data. The GHS, later the GLS and identified in Chapter 2, was an annual individual-level survey of UK households aiming to capture data on a range of topics including health and lifestyle, as well as income, education, migration, and other demographic information [443]. The survey ran from 1972 to 2012; the 2006 dataset was the latest available at the time of analysis without a Special Access Licence [443], and importantly was aligned with available detailed hospital admissions and mortality data [265].

Two key variables were utilised from the dataset: '*estimated weekly units*' was used to capture mean alcohol consumption; '*total units on the day in which the most alcohol was drunk*' was used to represent peak consumption. A total of 13,894 adults had data for both key variables, excluding outliers (those reporting >300 units per week or >60 units peak daily consumption). Different measures were generated from these data: mean and peak alcohol consumption estimates for at-risk drinkers and those that are not at risk were needed for the analysis, by age category and gender. Table 54, describing these data, can be found in Appendix E.

Our elderly men (aged 75 years and over) are assumed to have a distribution of mean alcohol consumption as described by the GHS 2006 data, and shown in Table 23:

Table 23: Distribution of mean alcohol consumption, males 75 years and older, GHS 2006

Mean daily units	None	Less than 4	4 to less than 8	8 to less than 12	12 to less than 16	16 or more
Percentage of sample	15.99%	72.05%	9.94%	1.40%	0.31%	0.31%

Converting mid-point intake for the categories in Table 23 into grams, and using abstainers as the reference group ($RR = 1$), the relative risk of lip, oral and pharyngeal cancer was calculated for each of these categories using equation (48).

This produced estimates of RR =1.49 for drinking up to 3.99 units per day, RR =2.99 for drinking 4 to 7.99 units per day, RR =5.33 for drinking 8 to 11.99 units a day, RR =8.40 for drinking 12 to 15.99 units a day and RR =13.19 for drinking 16 to 23.99 units a day. Given there are 8g in a UK unit of alcohol, and the mid-point of the 0 to 3.99 units per day category is 16g per day, equation (49) describes the RR calculation for elderly male drinkers who consume under 4 units a day:

$$e^{0.02572(16)-0.00006(16^2)} = 1.49\ (2dp) \tag{49}$$

The AAF for lip, oral and pharyngeal cancer for males aged 75 and over was then calculated as 0.40 as follows, using equation (42) and with reference to data in Table 23. The denominator of equation (42) was calculated as 1.67 as follows:

$$1.67 = 1 + 0.1599(1-1) + 0.7205(1.49-1) + 0.0994(2.99-1) + 0.014(5.33-1) + 0.0031(8.4-1) + 0.0031(13.19-1)$$

The AAF for lip, oral and pharyngeal cancer for males aged 75 and over was then estimated to be 0.40 using the following calculations:

$$\frac{0.7205(1.49-1)}{1.67} = 0.2098$$
$$\frac{0.0994(2.99-1)}{1.67} = 0.1187$$
$$\frac{0.0140(5.33-1)}{1.67} = 0.0363$$
$$\frac{0.0031(8.40-1)}{1.67} = 0.0137$$
$$\frac{0.0031(13.19-1)}{1.67} = 0.0226$$

$$\boldsymbol{AAF} = 0.2098 + 0.1187 + 0.0363 + 0.0137 + 0.0226 = \mathbf{0.40}(2dp)$$

Mean and peak alcohol consumption across the GHS sample by age, gender and drinking status is shown in Table 55 and Table 56 of Appendix E. For males aged 75 and over, the average daily intake of alcohol was 41.99g among at-risk drinkers. According to the relationship described by equation (48), this corresponds to a relative risk of 2.65:

$$e^{0.02572(41.99)-0.00006(41.99^2)} = \mathbf{2.65}\ (2dp)$$

In line with NHS guidelines on safe drinking [444], it was assumed that individuals drinking under the current average daily drinking guidelines (three units a day for men; two for women) were not at an increased risk of chronic conditions.

For partially-attributable acute conditions, there is a general lack of epidemiological studies linking different alcohol consumption levels to harm for each condition [445]. In the absence of such data, it was possible to estimate RR functions from the distribution of alcohol consumption across the population and AAF estimates, again using the relationship described in equation (42).

The AAF estimates for the thirteen partially-attributable acute conditions in the model were taken from the NWPHO report [265]. GHS data was again used to capture the distribution of alcohol use in the English population, but because these conditions are more closely linked to binge drinking behaviour, and following Purshouse *et al* [253], *peak*, rather than *mean* alcohol consumption was used.

Increased risk of acute conditions was assumed to start from peak consumption levels of three units in a day for women; four units in a day for men. This is somewhat lower than the 'loose' marker for binge drinking used in the UK of more than double the recommended daily intake in one session [446, 447]. However, these thresholds were reasoned as appropriate with the belief that heightened risk for many acute conditions begins before six and eight units in a session, respectively for women and men. The legal blood alcohol content for being in charge of a vehicle is difficult to translate into binge units as it depends on physiological factors, but quick ingestion of four units of alcohol will likely increase the risk of acute conditions for an average male. Similar thresholds for acute condition risks were used in the SAPM [253].

The functional forms of the estimated relative risk equations for acute partial conditions were assumed to be linear, in the absence of evidence in the literature [445], and following previous work [253]. The generic equation for a relative risk function of this type can be defined as follows:

$$\begin{aligned} RR &= 1 + \beta(c - \tau) \quad if\ c > \tau\ , \\ &= 1 \qquad\qquad\quad otherwise \end{aligned} \tag{50}$$

where c represents peak consumption and τ is the risk threshold; these equations were estimated in Microsoft Excel using the Solver tool.

7.3.2.2. Conditions wholly attributable to alcohol

For the thirteen wholly alcohol-attributable conditions in the model, the risk of hospitalisation and death is zero if no alcohol is consumed. The approach to estimating these risks was therefore necessarily different to the approach used for partially-attributable condition risks. *Absolute*, rather than *relative* risk functions were needed to link alcohol use to morbidity and mortality risk. As for partially-attributable conditions, three types of risks were needed:

1. Risk of hospital admission for each condition
2. Risk of death following hospital admission for each condition
3. Risk of 'spontaneous' death for each condition

Published work quantifying the link between alcohol use and wholly-attributable alcohol condition harm is limited [265, 448, 449]. The risk of hospitalisation for each of the thirteen conditions was estimated using the hospital admissions data in Table 51 and the distribution of alcohol consumption in the GHS data. As above, *mean* consumption was used for chronic conditions, *peak* consumption for acute conditions. Risk functions were again assumed to be linear, in line with previous work [253], and can be described by the following equation:

$$\begin{aligned} risk &= a + b(c - \tau) \quad if\ c > \tau\ , \\ &= 0 \qquad\qquad\quad otherwise \end{aligned} \tag{51}$$

where c and τ again represent consumption and the risk threshold, respectively, and a and b are parameters to be estimated. The Solver tool in Microsoft Excel was used to estimate equation parameters, by age group, gender and condition.

Alcoholic liver disease (ALD) is one of the more prevalent conditions wholly attributable to alcohol, with 12,373 patient-specific hospital admissions in the year ending March 2006 (Table 51). For ALD, the HES-ONS data showed 3,298 ninety-day deaths linked to 14,886 admissions. The NWPHO report recorded 3.59% of deaths and 4.22% of hospital episodes for ALD to be attributable to males aged 75 and over. The death risk after hospitalisation was therefore calculated as follows:

$$\frac{(3{,}298)x(0.0359)}{(14{,}886)x(0.0422)} = 0.19\ (2dp)$$

The number of spontaneous deaths could then be estimated using equation (45), in an identical manner to partially-attributable conditions. Absolute risk for spontaneous death could then be estimated as a linear function, using this number and the distribution of alcohol consumption, using the same process as described equation (51) and the accompanying text.

This concludes the description of the many alcohol-related risks faced by simulated individuals in the BIT model, and the methods used to estimate these risks. It remains to describe quantification of cost and health outcomes in the model.

7.3.3. Costs

Costs of hospital admissions for each alcohol-related disease in Table 22 were taken from the SAPM report, and were originally derived from work by the Department of Health on the cost to the NHS of alcohol-linked diseases [450]. These costs comprise the costs of: hospital inpatient and outpatient visits; accident and emergency visits; ambulance services; GP and Practice Nurse consultations; dependency prescribed drugs; specialist treatment services; and other health care [253]. These costs were inflated to 2011/2012 levels using the Unit Costs of Health and Social Care index for Hospital & Community Health Services Prices [451] and are shown in Table 59 of Appendix E.

7.3.4. Utilities

Baseline utility for patients with no current comorbidity were taken from the general population utility profile estimated by Ara and Brazier using Health Survey for England data [452].

The Health Outcomes Data Repository (HODaR) contains data EQ-5D scores for around 2,000 diagnoses, and was used to incorporate utility values into the SAPM [253]. The HODaR is the first to supplement routine clinically coded data from one UK Hospital Trust (Cardiff and Vale) with survey data including demographic information and utility values [453]. Using this one source to capture utility for all 47 alcohol-linked conditions in the model has the clear advantage of avoiding bias and variability between studies. Mean utility for each condition was taken from this resource.

Where utility data were not available, mean utility was assumed to be that of similar conditions, following the SAPM [253]. The mean utility for mental and behavioural disorders and alcohol-induced Cushing's syndrome were assumed similar to alcoholic polyneuropathy; utility for methanol poisoning as assumed similar to ethanol poisoning; utilities for air, space and water transport accidents were assumed similar to road traffic accidents; utilities for firearm injuries, fire injuries, drowning and excessive cold were assumed similar to pedestrian traffic accident [253].

In HODaR, the mean age was 59 among inpatient, and 58 among outpatient, respondents [453]. EQ-5D scores generally decreased with age and number of comorbidities [453].

In HODaR, utility values are at 6 weeks post-discharge. The first two weeks following hospital admission are assumed to have zero utility. Following this, the HODAR utility values are applied for the next ten weeks for acute conditions and are used to represent ongoing utility for chronic model conditions. The absence of other time points in the dataset is a limitation of HODaR for this purpose, and it is not clear whether this will over- or under-estimate health gains from avoiding model conditions, particularly acute conditions. Condition-specific utility values are shown alongside costs in Table 59.

7.3.5. Limitations

Though based on established work in the field, there are some limitations of these methods to link alcohol use to health. Firstly, there is uncertainty around RR functions for conditions partially attributable to alcohol. For partially attributable conditions, RR functions from the literature were used. These were often based on meta-analyses using data from populations outside of the UK, and the transferability of these estimates to a UK population is unclear. But further, there will be uncertainty around the parameters of these RR functions, as well as uncertainty around the functional forms of the RR equations fitted. This uncertainty will be reflected in uncertainty around AAF estimates generated from the relationship described in equation (42), risk estimates of hospitalisation and and death that are inputs in the BIT model, and ultimately model outputs. This is a limitation of this work, previous leading economic evaluations of alcohol strategies [253, 425] and has been a limitation of the established field of work linking alcohol use to health [454]. Recent research has developed methods to estimate uncertainty around AAFs [454]; this should improve the usefulness of future economic evaluations in the area.

Secondly, the alcohol-related morbidity data is based on hospital admissions only, and does not account for the burden of patients treated for alcohol-related conditions in primary care alone. The greater burden will come from more serious diseases which require hospital admission, so this is considered a minor limitation, and should lead to conservative estimates as the overall benefit of reducing alcohol use.

Thirdly, the appraoch taken does not account for relationships between risks for the various conditions in Table 22. Diabetes is known to increase the risk of chronic liver disease [455]; there are likely to be numerous links between risks for conditions in the model that are not accounted for. For the case of diabetes and liver disease, ignorance of an interaction in risk will lead to underestimation of the benefits of reductions in alcohol use. In other cases there might be an inverse relationship between risks: suffering the effects of a stroke often impairs ability to drive, and non-driving may lower the risk of a road traffic accident [456].

Fourthly, there were several limitations to the methods to link hospitalisation to temporary heightened risk of death. As noted above, the HES-ONS linked data and TARN data linking hospital admissions to mortality were not age-, gender-, or patient-specific, and not always specific to the disease categories in Table 22. Lack of patient specificity means while there can only be one recorded death per patient, there could have been multiple hospital admissions for every patient in the data. The 90-day death rate is likely underestimated for some conditions; this should understate the mortality gains from alcohol use reduction. Lack of disease-specificity in the TARN database meant the same 90-day mortality rate was assumed across all partially attributable acute conditions; this may have led to overestimation of the 90-day mortality for some, or even all of these conditions, if other conditions classified as trauma conditions in the TARN database have higher mortality after hospital admission.

Ninety-day death statistics were conservatively read as 'death at 90 days after admission', when all that is known is death occurred in the first 90 days after admission. This was considered a minor and conservative assumption, as the mortality benefits of alcohol use reductions will be slightly understated as a consequence.

Greater efforts could have been made to accurately capture the heightened health risks for each condition in Table 22, but understanding the prognoses of patients hospitalised for alcohol-related conditions is far from simple. The first challenge is the range of conditions: there are twenty nine chronic and eighteen acute conditions listed in Table 22; understanding prognosis following hospitalisation for each would be an expensive task. The second challenge is that many of the conditions are actually groups of conditions, with varying prognosis by type. Alcoholic liver disease, for example, is an umbrella term incorporating fatty liver disease, alcoholic hepatitis and the more serious form of the disease, alcoholic cirrhosis. Time to death for alcoholic liver disease patients is further mediated by age and future alcohol use, among other factors [457]. Malignant neoplasm of colon is one of the more specific condition categories in Table 22, but published evidence shows prognosis to vary significantly by treatment which is applicable to only the 10-20% of all patients who develop hepatic involvement of colorectal origin [458].

There are numerous factors determining prognosis in cancers, including cancer stage and type and treatment options, which are often interrelated, making it difficult to characterise average prognosis. Hypertensive diseases, to use another example, can lead to death from cardiovascular disease or kidney damage, with a varied prognosis that is influenced by the behaviour of a patient [459, 460]. It is unclear whether taking a more simplistic approach to capture heightened death risk after hospitalisation has led to under- or over-estimation of the mortality benefits of alcohol use reduction; the import for the results of the cost-effectiveness analysis in Chapter 8 will likely be minor.

7.3.6. Summary

This section has described calculation of alcohol-related condition morbidity and mortality risks, and risks of death from causes unrelated to alcohol or tobacco use, for use in the BIT model described previously. This approach is largely based on established methods, from publications that have been used to inform UK Government decision makers [253], but has several limitations, discussed above. Overall, it is believed that these methods are useful and detailed and sufficiently capture the link between alcohol use and health consequences for the purposes of this thesis.

7.4. Chapter Summary

This chapter has been largely descriptive; the chapter aims of describing to the reader (i) the BIT model and (ii) the data and methods to link alcohol use status to health, have hopefully been achieved.

The strengths and limitations of the methods described have been detailed. The BIT model is an improvement on existing models of the health economic consequences of smoking cessation strategies reviewed in Chapter 3 and including the smoking model recreated in the Chapter 6, in that individual patients are followed through a flexible modelling platform, allowing more flexibilityand accuracy in capturing long-term behaviour and interaction between alcohol use and smoking status. The model still bears limitations, such as assumptions about future quit attempts, the treatment of time as discrete and the assumption of no interaction between indviduals.

The methods to link alcohol use to health consider a wide and established battery of conditions with links to alcohol use, and follow established methods from the field. Limitations have been noted, including the absence of assessment of uncertainty around estimates, and ignorance of the effect of alcohol use upon patients who seek primary care but are not admitted to hospital.

The mechanism and model inputs for the BIT model should now be clear. Chapter 5 established the method to predict 'next year' smoking status and at-risk drinking status for an individual, using the bivariate dynamic econometric equations estimated therein. Chapter 6 described the methods and data to link smoking status to health and health related costs and quality of life. Chapter 7 has established the data and methods to link alcohol use to health, healthcare costs and health related quality of life, and described a simulation model to incorporate all of these inputs. The next and penultimate chapter of this thesis sets out the plan of analysis of the BIT model, and reports results. Within Chapter 8, the answers to the key research questions of this thesis should become clear.

8. Chapter 8: Economic appraisal of competing strategies to aid smoking cessation using the BIT model

8.1. Introduction

The methods and data of the BIT model now described, Chapter 8 presents and analyses results from an economic appraisal of competing strategies to aid smoking cessation, using the BIT model. The decision problem is identical to that posed in Chapter 6; the competing strategies assessed are standard courses of cytisine and varenicline.

The key aim of this chapter is to explore the consequences of using projections of long-run behavioural patterns from panel survey data, which incorporate inter-behavioural links, within an individual-level simulation modelling framework for economic appraisal outcomes. This is achieved with comparison of BIT model results with standard practice model results from Chapter 6.

Chapter 8 begins with a note on performing economic appraisals using the BIT model. Results from the BIT model are then presented. Evidence from internal validation tests set out the mechanics of the model, before key results from the economic appraisal are analysed. The implications of assumptions about long-term behaviour for model results are shown to be substantial. The penultimate section of this chapter discusses the results and their implications for future work, before the findings are summarised.

8.2. Performing cost-utility analyses with the BIT model

When the model is used to compare competing interventions, for transparency and efficiency, one full run of the model comprises four separate runs of model "branches", where in each branch individuals enter the model as either (i) non-smokers and not at-risk drinkers; (ii) smokers but not at-risk drinkers; (iii) non-smokers but at-risk drinkers; (iv) smokers and at-risk drinkers. The behaviour characterised by individuals in these four branches as they enter the model is

labelled “NAR, NS”, “NAR, S”, “AR, NS” and “AR, S” respectively in Table 24, as in the previous chapter.

Table 24: Group labels for behaviour upon entry

Smoking and drinking status on model entry	Entry Group
1, Not an at-risk drinker, Non-smoker	NAR, NS
2, Not an at-risk drinker, Smoker	NAR, S
3, At-risk drinker, Non-smoker	AR, NS
4, At-risk drinker, Smoker	AR, S

Effectiveness data can then be applied to set the proportions of the cohort in each of the four behavioural categories, subject to the effectiveness of the intervention. Accordingly, for an aid to smoking cessation with a 12 month quit rate of 50%, one would apply weights of 0.5 to results from non-smoking starting points, and 0.5 to results from smoking starting points. To weight the results appropriately for smoking *and* drinking starting points according to groups 1 to 4 in Table 24, the distribution of drinking across at-risk and not at-risk categories is taken from GHS 2006 data [461]. Among adult smokers, 35.78% drink to at-risk levels. In this hypothetical situation therefore, a weight of 0.179 (=0.3578 x 0.5) would be applied to group 3 results and group 4 results, and a weight of 0.321 (= (1-0.3578) x 0.5) would be applied to group 1 results and group 2 results.

Evidence detailed in Chapter 2 suggests dopamine-inhibitor drugs such as cytisine and varenicline make alcohol less enjoyable [67, 68]. Chapter 5 results suggested that a smoking cessation intervention may have a direct negative influence upon the propensity to drink to at-risk levels, whether the intervention is successful or not. However, as neither of these effects would influence the relative proportion of at-risk drinkers in each arm of the appraisal, adjustments were not made to the model.

To account for the different age profiles of those above and below at-risk drinking thresholds, age distributions for smokers by gender and drinking status are used

and drawn from as individuals enter the model. These distributions are reported and described in Table 49 of Appendix E and the accompanying text. Of course, once this 'age profiling' adjustment is made, patients are no longer identical across the four groups in Table 24. Age, and consequently time to death from causes not linked to alcohol use or smoking, differ for the *n*th individual across the four groups. This introduces variability across the four Table 24 model entry groups, but is necessary for the incremental analysis. To validate the model, introducing such variability was not necessary, and during model validation the *n*th individual to enter the model was identical across the four model entry groups. The next subsection reports some results from this validation process.

8.3. Model Results

8.3.1. Model Validation

The validation process involved two key stages. First, key results were generated at various restricted model specifications, using 10,000 simulated persons, to test the mechanics of the model. Following this, the number of simulated persons needed to generate sufficiently accurate results from a model run was analysed.

8.3.1.1. Testing aspects of the model mechanics

To test and internally validate the BIT model, key outputs were assessed across different specifications. Four validation checks were made, beginning with Validation 1. For the initial validation, it was useful to restrict movement across behavioural groups. Initially, the two key behaviour-related consequences in the model, behaviour-related morbidity and behaviour-related mortality, were also nullified. Table 25 shows key per-person results from the 'Validation 1' specification. As expected, simulated individuals incur no morbidity-related costs. Similarly, as behaviour-related health consequences have been nullified, life years and QALYs are identical across the four entry groups. Average utility is high, at 0.89, as expected in the absence of morbidity decrements.

Table 25: Per Person Discounted Model Results, Validation 1

No behaviour change, no behaviour-related morbidity, no behaviour-related mortality				
	Model Entry Group			
	NAR, NS	**NAR, S**	**AR, NS**	**AR, S**
Costs	£ -	£ -	£ -	£ -
Life Years	20.17	20.17	20.17	20.17
QALYs	17.88	17.88	17.88	17.88

Validation 2 differs from Validation 1 only in that behaviour-related morbidity was incorporated. As our simulated individuals were now subject to behaviour-related illness, it was expected that (i) overall utility would fall, (ii) per patient costs would be highest in the least healthy model entry group and lowest in the most healthy model entry group and (iii) per patient QALYs would be lowest in the least healthy model entry group and highest in the most healthy model entry group.

Table 26 shows key results from Validation 2. The results are as expected. Utility across the four model entry groups is significantly lower than in Table 25, despite LYs remaining constant. QALYs are highest and costs lowest in the healthy "NAR, NS" model entry group, who in this specification abstained from smoking and drinking over guidelines levels throughout their simulated lives after entering the model. The model entry group who smoked and drank above guideline levels for the remainder of their simulated lives paid the price, with the lowest utility and highest healthcare costs of the four groups.

Per person QALYs in the "AR, NS" entry group are lower than in the "NAR, S" entry group. This is explained by the extensive range of alcohol-related health conditions incorporated, in comparison to the limited key smoking-related chronic diseases included in the analysis, and does not necessarily imply that at-risk drinking is on average more dangerous than smoking. The imbalance between coverage of alcohol-related health conditions and smoking-related health conditions in this analysis is a limitation, but it is not expected to bias results of an

economic appraisal of aids to smoking cessation. Underestimation of the health consequences of smoking may understate the relative effectiveness of more effective smoking cessation strategies; this is also the case for the many economic appraisals reviewed in Chapter 3.

Table 26: Per Person Discounted Model Results, Validation 2

No behaviour change, no behaviour-related mortality				
	Model Entry Group			
	NAR, NS	**NAR, S**	**AR, NS**	**AR, S**
Costs	£ 16,854.12	£21,780.37	£ 18,200.46	£ 23,390.68
Life Years	20.17	20.17	20.17	20.17
QALYs	13.93	13.62	13.44	13.18

Validation 3 differs from Validation 2 in that behaviour-related mortality was incorporated. Simulated individuals were still restricted to the behavioural states they entered the model in, but now also faced the most severe health consequences of their alcohol use and smoking status. It was expected that per patient LYs would reduce in all four model entry groups, and be highest in the healthiest group. In addition, it was expected that per patient QALYs would reduce further in comparison to the results from Validation 2, reflecting fewer life years. Per patient costs were expected to be lower in each group than in Validation 2, as the simulated individuals' shortened life span restricted their time accumulating healthcare costs.

Table 27 shows results from Validation 3. Results are again as anticipated. There are smaller differences between entry group-specific costs in Table 27 than in Table 26. This is explained by those in healthier model entry groups living longer than those in less healthy model entry groups, allowing them more time for behaviour-related condition incidence. Differences in per patient QALYs between entry groups are slightly greater in Table 27 than in Table 26, due to the higher per person LYs in healthier groups in Table 27.

Table 27: Per Person Discounted Model Results, Validation 3

No behaviour change				
	Model Entry Group			
	NAR, NS	**NAR, S**	**AR, NS**	**AR, S**
Costs	£ 9,858.96	£ 11,789.88	£ 11,023.74	£12,887.23
Life Years	17.95	17.67	17.65	17.46
QALYs	13.25	12.89	12.70	12.45

Validation 4 is the full model specification, and differs from Validation 3 in that individuals were no longer restricted to the behavioural states in which they entered the model. It was anticipated that the results would be similar to those in Table 27 in that results from those in healthier model entry groups would have better outcomes than those in less healthy model entry groups, but that differences between model entry groups would be smaller.

Table 28 shows results from Validation 4. The results are generally as expected; those in the "NAR, NS" model entry group have the lowest costs and the best health outcomes, while those in the "AR, S" model entry group have the highest costs and worst health outcomes. Differences between "NAR, NS" and "NAR, S" and between "AR, S" and "AR, NS" are small, implying that the lifetime health benefit of entering the model as a smoker as opposed to a non-smoker is small.

Table 28: Per Person Discounted Model Results, Validation 4

Unrestricted model				
	Model Entry Group			
	NAR, NS	**NAR, S**	**AR, NS**	**AR, S**
Costs	£ 10,791.55	£ 10,983.04	£ 11,448.68	£11,755.97
Life Years	17.76	17.75	17.61	17.6
QALYs	12.82	12.79	12.47	12.42

8.3.1.2. Appropriate numbers of simulated individuals for the analysis

At this point, results of the economic appraisal problem comparing cytisine to varenicline as an aid to smoking cessation come in to focus. Consequently, the 'age profiling' adjustment described above was used to account for the differing age distributions of at-risk drinkers and others in results presented from here onwards. As this introduces necessary variability across individuals run through the four model entry groups in Table 24, comparison of results across these groups becomes less meaningful. Results are from here presented separately for different smoking cessation strategies only.

Before generating final model results to make inference about policy for the target population, it was necessary to establish the number of simulated individuals needed before results stabilised. There is a trade-off between accuracy and feasibility in that both accuracy and model run time increase with the number of simulated persons run through the model. Key results of interest presented are the discounted per person costs, QALYs and NB of cytisine versus varenicline as an aid to a smoking cessation attempt, assuming a willingness to pay of £20,000 for an additional QALY. Figure 16, Figure 17 and Figure 18 show the relationship between number of individuals run through the model and these three respective results.

The results are highly variable up to around 7,000 simulated persons, then stabilise somewhat. Per person costs do though continue to increase very gradually as more per-patient results are added, while per person QALYs fall very

gradually, up to around 22,000 persons. Reflecting these trends, the INB of cytisine over varenicline is fairly stable after 7,000 simulated persons but increases up to the point where results for 22,500 simulated individuals have been collected. After this point, the results in Figure 16, Figure 17 and Figure 18 do seem to stabilise. For all results of the economic appraisal presented in the next subsection, 23,000 simulated persons were run through each model entry group.

Figure 16: Relationship between Per Person Total Discounted Costs and Number of Simulated Persons

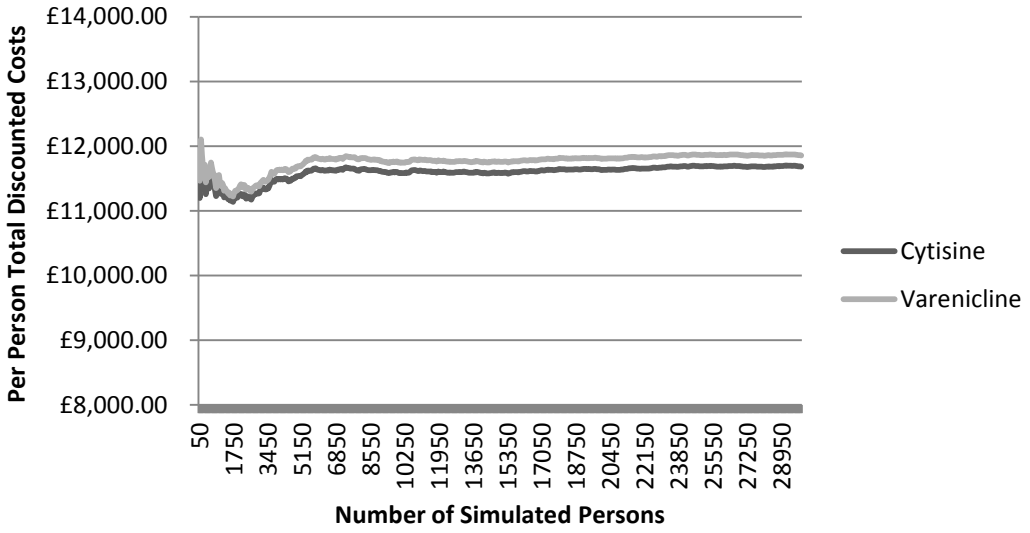


Figure 17: Relationship between Per Person Total Discounted QALYs and Number of Simulated Persons

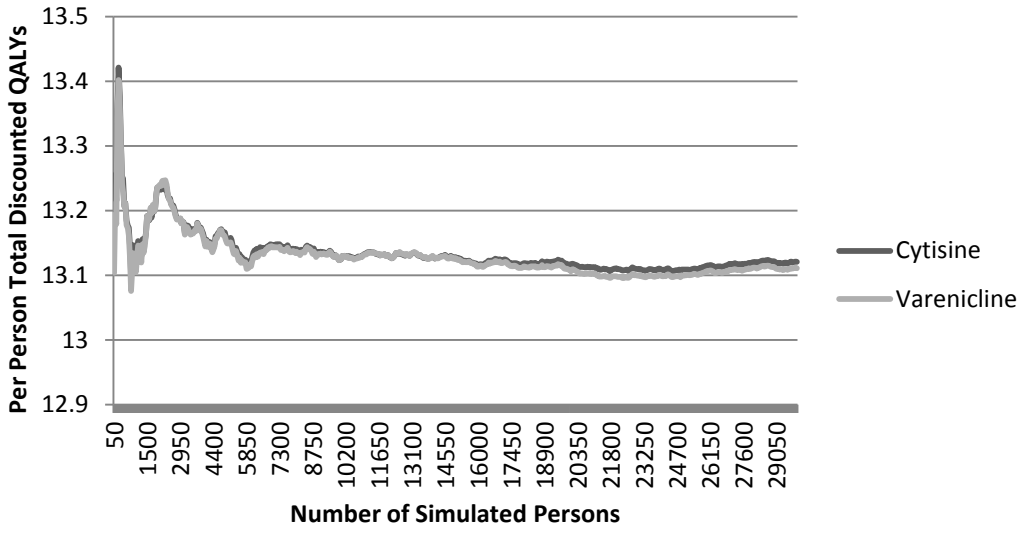
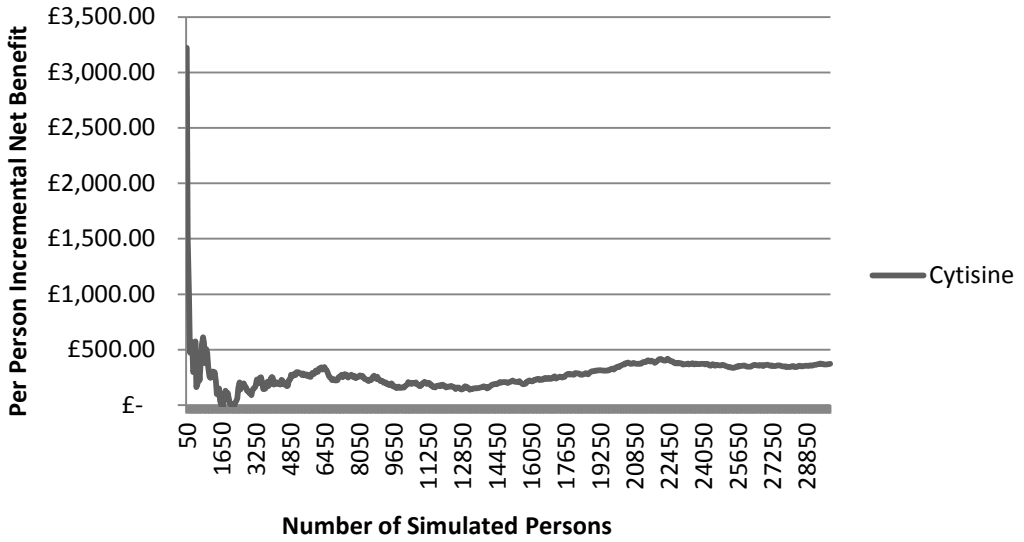


Figure 18: Relationship between Per Person INB of Cytisine and Number of Simulated Persons, at a willingness to pay threshold of £20,000 per QALY gained



8.3.1.3. Validation Summary

This validation has foremost demonstrated that the BIT model described in Chapter 7 produces expected and sensible results. Key to this was demonstrating results with different assumptions in place. The validation process included evaluation of the appropriate number of simulated persons to use in the economic appraisal. There was a trade off between accuracy and computational expense,

and 23,000 people per model run were believed to be appropriate. Results from the economic appraisal of cytisine as an aid to smoking cessation using the BIT model can now be presented.

8.3.2. Economic Appraisal Results

8.3.2.1. Probabilistic Results

Table 29 shows mean PSA results from the economic appraisal of cytisine versus varenicline as an aid to smoking cessation, using the BIT model. As in Chapter 6, the results of the PSA are presented as the primary results of interest, as unlike deterministic estimates, they take into account the distributions of input parameters and interaction between parameters, and thus are the more accurate estimates. One run of the individual-level BIT model was far more computationally expensive than one run of the standard practice model of Chapter 6; it was therefore not possible to perform a vast number of PSA runs. The results in Table 29 are based on 750 PSA runs.

Table 29: Mean PSA discounted results, compared to equivalent results from Chapter 6

Treatment	Costs		Life Years		QALYs	
	Total	Incr.	Total	Incr.	Total	Incr.
BIT Model Results						
Cytisine	£ 11,700	-£164	18.471	0.002	13.119	0.003
Varenicline	£ 11,865		18.469		13.116	
Chapter 6 Results						
Cytisine	£ 4973	-£251	17.53	0.03	14.55	0.03
Varenicline	£ 5225		17.50		14.52	

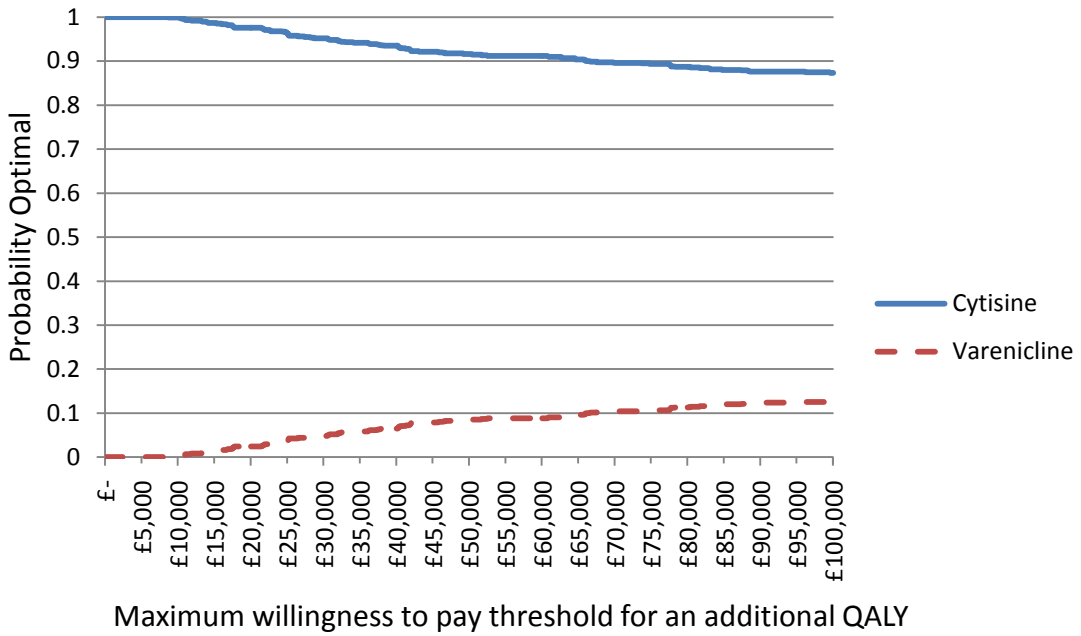
As in Chapter 6, the mean PSA results show cytisine to dominate varenicline, producing a higher number of per person LYs and QALYs and lower person total lifetime costs. Incremental LY, QALY and cost benefits of cytisine are much smaller than estimated by the standard practice cohort model, however. This is reflective

of relatively lower importance of model entry smoking status upon long-run behavioural patterns in the BIT model. Mean incremental HRQoL benefit of cytisine of 0.003 QALYs per person is slight, and a tenth of the estimated HRQoL benefit of cytisine from the standard practice model. Mean total cost difference between treatments is £164, a higher proportion of the corresponding estimate from the standard practice model, £251. However, these figures include a treatment cost difference of £147. Ignoring treatment costs, the per person total cost difference between strategies is £17 in the BIT model, compared with £104 in the standard practice model.

The mean ICER of cytisine versus varenicline is -£58,229. To estimate a confidence interval (CI) around the mean ICER, jackknifing was used. Jackknifing is a method for dealing with the bias caused by ratios [462]; the jackknifed 95% CI for the mean ICER is [-£67,560, -£48,027]. The jackknifed CI narrows as the number of PSA runs informing the mean increases, and so is also useful as a guide as to whether the number of PSA runs used is sufficient, which in this case it appears to be.

Figure 19 shows cost-effectiveness acceptability curves [412] for the two strategies. The probability cytisine is optimal is over 0.95 up to a willingness to pay threshold of £30,500 per additional QALY. This probability falls as the willingness to pay threshold increases. The curves appear similar to the corresponding CEACs from the standard practice economic appraisal.

Figure 19: Cost-effectiveness acceptability curves for cytisine and varenicline

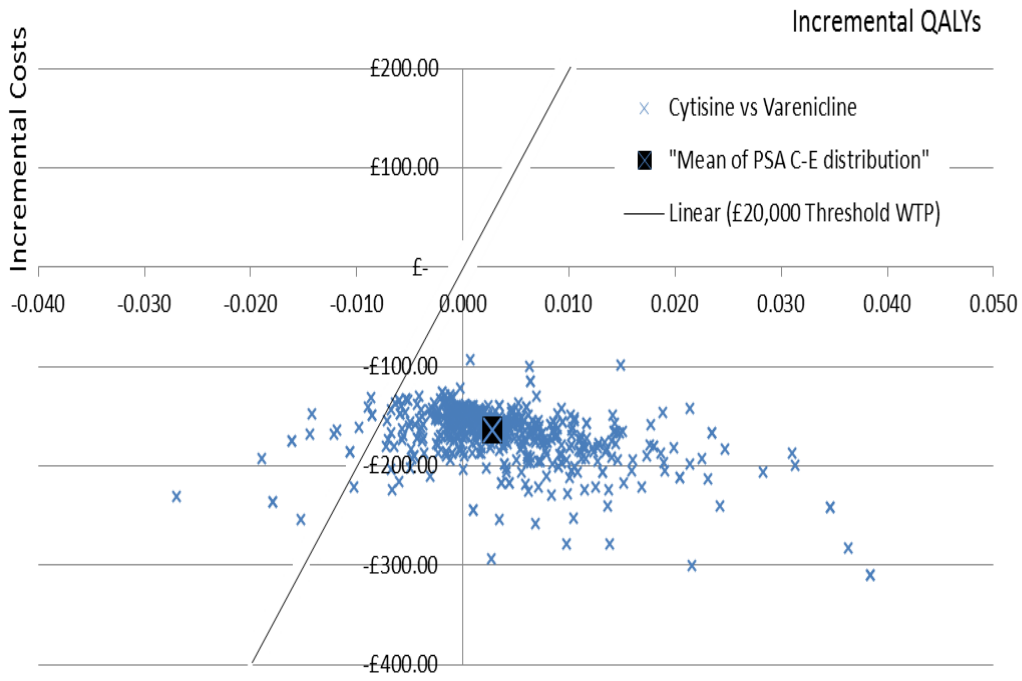


The distribution of the 750 PSA ICER estimates is shown in Figure 20. Nearly 70% of the estimates are in the south east quadrant, indicating that cytisine dominates varenicline. The remaining estimates are in the south east quadrant, indicating cytisine is less costly and less effective than varenicline. Over 95% of estimates are to the right of the £20,000 willingness to pay threshold for an additional QALY, favouring cytisine over varenicline at this threshold. Every ICER estimate in Figure 20 shows cytisine to produce lower total costs compared to varenicline. This is influenced by the relative treatment costs of the two strategies. Ignoring treatment costs, 17.5% of PSA ICER estimates show varenicline to be less costly than cytisine.

The correlation between incremental costs and incremental QALYs is not as strong as in the equivalent Figure 13 from Chapter 6. This is a consequence of the small QALY and non-treatment cost differences between those entering the model as smokers and those entering the model as non-smokers. In the standard practice appraisal deterministic sensitivity analysis, intervention effectiveness was shown to be the key determinant of model outcomes. As treatment effectiveness has a weaker association with long-term outcomes when HILDA data on longitudinal behaviour is used in place of simple assumptions which favour high short-term

effectiveness, this parameter appears to have less influence over BIT model outcomes.

Figure 20: Scatter plot of results from 750 PSA runs



8.3.2.2. Sensitivity to Treatment Cost

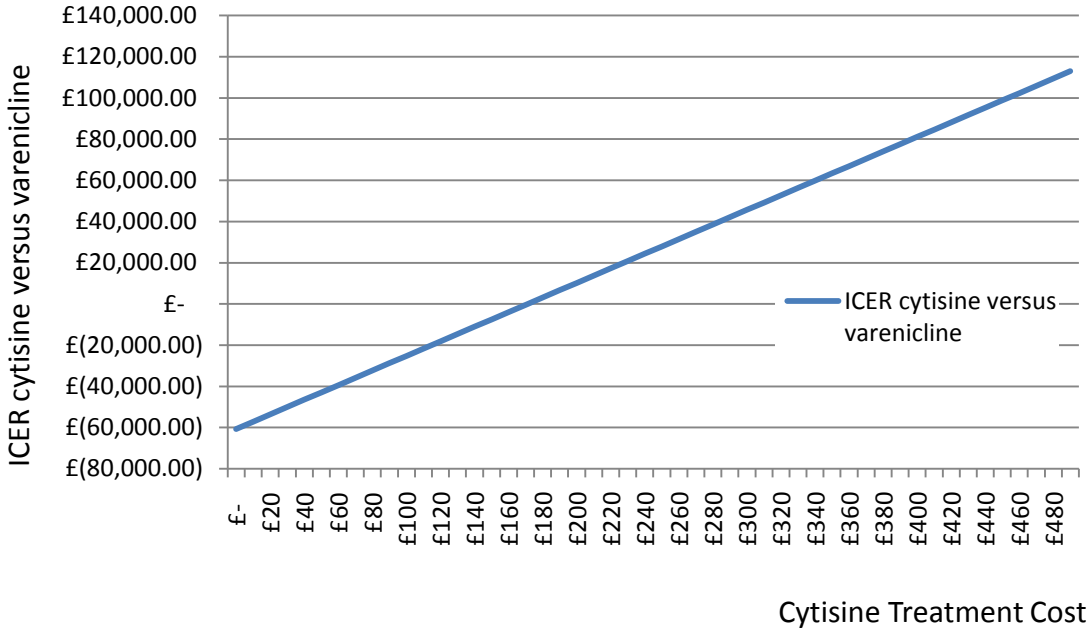
Due to the way the BIT model is structured, whereby treatment cost data are retrospectively applied to model output in order to calculate economic appraisal outcomes, it was possible to analyse the sensitivity of results to treatment cost using the probabilistic output. This is particularly pertinent to the appraisal of cytisine for smoking cessation as the cytisine cost estimate if adopted for use within the NHS is uncertain.

Figure 21 illustrates how the mean PSA ICER changes as the assumed treatment cost of cytisine increases. At the estimated treatment cost of £16.79, cytisine dominates varenicline as the cost saving and more effective alternative. However, the mean incremental cost savings for cytisine at this treatment cost are only £164, as shown in Table 29. As the assumed treatment cost of cytisine rises in Figure 21, the incremental cost savings of cytisine falls by the same amount. Cytisine treatment need only cost £18 more than varenicline (just over £181) for the estimated mean cost saving of cytisine (due to better health outcomes) to be eradicated. Were cytisine treatment to cost £240, varenicline would be preferable

to cytisine at a willingness to pay threshold of £20,000 for an additional QALY; were cytisine treatment to cost £270, varenicline would be preferable to cytisine at a willingness to pay threshold of £30,000 for an additional QALY.

Of course, the treatment cost of cytisine, were it to be adopted for use within the NHS, is likely to be well below the treatment cost of varenicline. As reported in Chapter 6, as of March 2013 it was possible in the UK to buy a standard course of Tabex (active ingredient cytisine) online for £16.79 [403]. Figure 21 is mostly useful in demonstrating that as treatment effectiveness differences between smoking cessation strategies lead to only small differences in mean health and health-related cost outcomes in the BIT model, the respective treatment costs of strategies are important in influencing strategy appraisal decisions.

Figure 21: Relationship between cytisine treatment cost and cost-effectiveness



8.3.2.3. Deterministic Sensitivity Analysis

The importance of other model inputs was tested with univariate sensitivity analysis of the deterministic results. Table 30 shows mean baseline deterministic results, alongside results from different sensitivity analyses. The deterministic mean per person discounted costs, LYs and QALYs are similar to corresponding

mean PSA estimates, though the deterministic incremental cost and health benefits of cytisine are slightly higher.

Table 30: Deterministic Sensitivity Analysis Results

Variable	Sensitivity analysis	Treatment	Costs		LYs		QALYs	
			Total	Incr.	Total	Incr.	Total	Incr.
Baseline		Cytisine	£11,666	-£174	18.456	0.008	13.109	0.010
		Varenicline	£11,840		18.448		13.099	
Difference between treatment effectiveness (cytisine minus varenicline)	Upper 95% CI value	Cytisine	£11,608	-£237	18.473	0.027	13.131	0.033
		Varenicline	£11,845		18.447		13.088	
	Lower 95% CI value	Cytisine	£11,725	-£136	18.439	-0.003	13.088	-0.004
		Varenicline	£11,861		18.442		13.092	
Assuming cytisine intervention affects unobserved time-invariant attributes which determine propensity to smoke	Alpha shifts 10% left	Cytisine	£11,617	-£224	18.479	0.031	13.124	0.025
		Varenicline	£11,840		18.448		13.099	
	Alpha shifts 20% left	Cytisine	£11,621	-£220	18.535	0.087	13.170	0.071
		Varenicline	£11,840		18.448		13.099	
	Alpha shifts 50% left	Cytisine	£11,528	-£313	18.568	0.120	13.196	0.097
		Varenicline	£11,840		18.448		13.099	
Ignoring interrelation between behaviours		Cytisine	£11,546	-£157	18.475	0.005	13.153	0.006
		Varenicline	£11,704		18.470		13.147	
Ignoring dynamics		Cytisine	£11,313	-£175	18.557	0.009	13.256	0.012
		Varenicline	£11,488		18.548		13.245	

Of the various specifications of the standard practice model tested in Chapter 6, only analysis of uncertainty around the relative effectiveness of cytisine affected the adoption decision. This analysis was repeated using BIT model results. As Table 30 shows, at the upper 95% CI of the relative effectiveness of cytisine, incremental gains from cytisine are over three times greater than baseline. At the

lower 95% CI of the relative effectiveness of cytisine, varenicline is more effective than cytisine, and this is reflected in greater total LYs and QALYs for varenicline. The relative effectiveness is still an important determinant of model outcomes. However, the ICER for varenicline at this specification is £33,574; cytisine is still preferable at willingness to pay thresholds below this level. In the corresponding specification in Chapter 6, the ICER for varenicline was under £8,000, indicating varenicline to be preferable at current UK willingness to pay thresholds.

The results presented up to now have shown short-term treatment effectiveness to have a diminished impact on long-run treatment cost-effectiveness when the former only has implications for state dependence in dynamic behaviour equations, in comparison to the standard practice model in Chapter 6 and numerous applications of a similar model structure where smoking status following a cessation attempt was assumed to be a stronger indicator of long-run behaviour [357-367]. However, as discussed in Chapter 5, smoking cessation interventions could have a greater influence over long-run smoking status and health outcomes, if the person-specific, time-invariant, unobserved characteristics which influence the propensity to smoke, termed alpha here for brevity, are affected by an intervention. Due to the flexibility of the dynamic equations and BIT model, it was possible to test the implications of such an effect here.

The person-specific alphas of the 23,000 simulated people in the model were reduced by (i) 10%; (2) 20%; and (3) 50%, in the cytisine treatment arm only, in three deterministic runs of the model. The results are shown in Table 30. If cytisine treatment was to permanently reduce the propensity to smoke by reducing alpha as well as leading to more short-run smoking quits than varenicline treatment, its relative superiority in terms of cost-effectiveness would be greater, and increasingly so as the effect upon alpha is increased. If smoking cessation interventions can permanently reduce the propensity to smoke, their value is greatly improved

The results so far have demonstrated implications of assumptions about long-term behaviour for the cost and health consequences of competing smoking cessation strategies. However, this has involved a contrast between simplistic modelling

assumptions about long-term behaviour, and more complex assumptions about the dynamics of smoking and its interrelation with alcohol use, based on longitudinal individual-level data. The key aim of this thesis was to better understand the consequence of a link between alcohol use and smoking for economic appraisals of competing behaviour change strategies. In an attempt to isolate this consequence, a deterministic run of the model was performed while setting the cross-state dependence variables in the dynamic behaviour equations, the variable relating to last year's smoking status in the drinking equation and the variable relating to last year's drinking status in the smoking equation, equal to HILDA sample means. This did not totally isolate the link between smoking and alcohol use, as the correlation between unobserved effects in the two dynamic equations captures part of the relationship. Nevertheless, due to the positive cross-state dependence parameters found in Chapter 5, it was anticipated that this would reduce the estimated incremental net benefit of cytisine relative to varenicline. Table 30 shows this to be the case; incremental health and health related cost gains are reduced in comparison to baseline. Total costs and QALYs are slightly lower in both treatment arms compared to baseline, suggesting some random variation affecting results, though as patients characteristics are fixed across interventions, this is less likely to influence incremental results. Of course, if a smoking cessation intervention can change the person-specific time-invariant characteristics which influence the propensity to drink to at-risk levels, its implications for long-run healthcare costs and HRQoL will be magnified. Chapter 5 suggested that these effects are positively correlated with person-specific time-invariant characteristics which influence the propensity to smoke, so this is plausible.

Using output from the dynamic analysis of longitudinal data on smoking and alcohol use in Chapter 5 to inform projections of long-run behaviour in this economic appraisal has influenced results, relative to results from the standard practice model in Chapter 6. There was a labour and computational cost to the econometric analysis presented in Chapter 5 however, which must be considered in the context of the applicability of the framework proposed in Chapter 1 for future work. For future economic appraisals of competing behaviour change strategies to investigate and quantify links to related health behaviours in the

absence of available data, the requisite skills and other resources will be required. This may form a practical barrier. It was therefore of interest to test the consequence of using simplistic analyses of the HILDA data to inform transitions between behaviour states, in place of the dynamic equations.

Confounded behaviour transition parameters were estimated by first sub-dividing the unbalanced panel of HILDA data, summarised in Table 3, Chapter 5, into gender and age-specific categories. Next, the distribution across smoking and non-smoking groups was summarised for those in each of the four behavioural categories in the BIT model in the last time period, for each age- and gender-specific category. The percentage of 'smoker' ('at-risk drinker') responses in a lagged-behaviour-, age- and gender-specific subgroup then comprised the probability of being a smoker (at-risk drinker) next year for that sub-group. To illustrate with an example, among men aged 19-25 who reported non-smoking and safe drinking last year, 228 of 2,419 responses reported current smoking. The probability of smoking next year for 18-24 year old male safe drinkers and non-smokers was therefore (228/2,419 =) 0.076. These confounded transition probabilities are reported in full in Appendix F, Table 60 and Table 61.

It was anticipated that using confounded transition probabilities would lead to broadly similar results to baseline, but show a greater incremental health benefit for cytisine. This was reasoned as the underlying data are driving the baseline behavioural projections, but results so far have indicated that unobserved heterogeneity was highly important in determining behavioural patterns over time in the baseline analysis. Table 30 shows incremental results using confounded transition probabilities to be very similar to baseline, with only marginally higher incremental health and financial gains for cytisine predicted. Again total costs and QALYs in both treatment arms are lower than baseline, suggesting random variation influencing results, though again this is less likely to influence incremental findings. These results suggest that using outputs from simple data analysis generates results that are a good approximation of results using full dynamic behavioural equations, in this case. However, the generalisability of this finding is not known, and the deterministic sensitivity analyses explored here have demonstrated the flexibility afforded by an appropriate dynamic and multivariate

approach to modelling longitudinal survey data, when applied to a flexible individual-level simulation cost-effectiveness model.

8.3.2.4. Calculation of the EVPI

The EVPI was calculated as the difference between the maximum INB obtainable and the expected INB of cytisine, as in Chapter 6, for willingness to pay thresholds of £20,000 and £30,000 for an additional QALY. Table 31 shows the per person EVPI for these thresholds, and the total EVPI assuming 1 million or 3 million smokers affected, across both the BIT model and the standard practice model of Chapter 6. The EVPI is lower in BIT model results, reflecting less uncertainty about the adoption decision at the willingness to pay thresholds considered, yet still high when applied to the total population likely to be affected by a decision regarding NHS aids to smoking cessation.

Table 31: EVPI for the adoption decision

	Expected Value of Perfect Information			
	BIT Model		Standard Practice Model	
	£20,000 threshold	£30,000 threshold	£20,000 threshold	£30,000 threshold
Per person	£2.23	£6.37	£11.71	£19.99
1 million affected	£2.23 million	£6.37 million	£11.71 million	£19.99 million
3 million affected	£6.69 million	£19.1 million	£35.13 million	£59.96 million

8.4. Discussion

Treatment effectiveness has been shown to have less influence over long-run costs and QALYs under BIT model assumptions than under standard practice model assumptions about long-run behaviour, demonstrated in the model presented in Chapter 6 and used in various published analyses [357-367]. This resulted in slight QALY gains and long-run cost savings for cytisine, in comparison to the less effective alternative varenicline. If the assumptions of the BIT model are robust, this may have implications for future modelling practice in appraisals of smoking

cessation strategies and for the validity of past economic evaluation studies. The differing methods and data in Chapters 6 and 8 have not changed the appraisal decision, but this is in large part because the evidence suggests cytisine has higher effectiveness and a lower treatment cost compared to varenicline; it is clearly the preferable alternative. Historically, novel pharmaceutical aids to smoking cessation have coupled evidence of higher 12 month cessation rates with higher treatment costs in comparison to existing alternatives, as was the case when varenicline emerged as a more expensive alternative to bupropion and NRT [366]. In such cases, recommendations from analysis using the BIT model may clash with recommendations from a standard practice model analysis. Given that standard practice assumptions about long-run behaviour have been shown to be based on limited evidence, it is important that assumptions and methods used in future models for the economic appraisal of competing smoking cessation interventions are robust and tested.

While the BIT model is designed to account for dynamic changes in behaviour, the model does not account for the difference in costs and consequences across treatment arms of subsequent aided quit attempts in simulated individuals who relapse to smoking, when the treatments available across arms may be different. As discussed in Chapter 7, because cytisine has a lower treatment cost and greater effectiveness than varenicline, the INB of cytisine may have been underestimated in this analysis. In cases where a novel smoking cessation strategy is more effective and more expensive than its comparators, it is unclear whether BIT model assumptions would favour one alternative over another. The importance of differences between treatment effectiveness and cost across strategies would assume more importance for appraisal results. Evidence on the effectiveness of pharmaceuticals in smokers who have previously relapsed after attempting to quit with the pharmaceutical aids would be welcome, and better data are also needed on risks for repeated quit attempts and choice of cessation aid in repeated quit attempts.

In the analysis, treatment effectiveness was an important predictor of cost-effectiveness, though other differences between treatments assumed more importance in determining appraisal results in comparison to the analysis of

Chapter 6. Sensitivity analysis showed cytisine need only cost £75 more than varenicline for varenicline to be preferable at a willingness to pay of £20,000 for an additional QALY. Aside from treatment cost, adverse events associated with competing treatments also assume greater consequence. Adverse events were not considered here, nor in past analyses, but there is some evidence of negative side effects from smoking cessation drugs. Cytisine compared with varenicline was found to have slightly lower risk of both headache and nausea in a recent meta-analysis of evidence [368]. There may be greater call to establish and utilise such evidence in future modelling studies.

The validation process highlighted an imbalance between coverage of alcohol-related health conditions and smoking health conditions in the model. Whereas the catalogue of alcohol-linked conditions established by the NWPHO is comprehensive [265], the five smoking-related diseases considered are a sub-sample of related conditions with great implications for healthcare burden [363]. Other diseases including bladder, pancreatic, kidney and stomach cancers, as well as hip fracture and periodontal disease have been linked to smoking for some time [463]. Omission of links to these diseases in the model will have understated the health benefit of smoking cessation, thus underestimating the importance of treatment effectiveness for smoking cessation. If greater emphasis is placed on justifying long-run behaviour assumptions in future NICE technology appraisals, any pharmaceutical company submitting evidence on the cost-utility of their novel aid to smoking cessation may be increasingly keen to highlight these links in their analysis.

Deterministic sensitivity analyses, exploiting the flexibility of the model, produced several interesting results. The importance of alcohol use for model outcomes was assessed, suggesting the relative cost-effectiveness of strategies with superior short-term effectiveness are under-estimated if the interrelated dynamics of alcohol and tobacco use are ignored. Uncertainty around relative treatment effectiveness was shown to be a key driver of results, though less important than in Chapter 6, where smoking status upon model entry was assumed to have greater implications for long-run tobacco use. The relative cost-effectiveness of one strategy versus another could however be great if those unobserved, time-

invariant, person-specific characteristics which are not observed in survey data but influence the propensity to smoke are changed to reduce said propensity permanently. This was demonstrated assuming cytisine had such an effect but varenicline treatment did not; however, this sensitivity analysis was not motivated by evidence to suggest that cytisine treatment should influence time-invariant characteristics to a greater extent than varenicline treatment. For this result to be meaningful in practice, information would be needed about the relative degree to which factors that may contribute to these characteristics are affected by different smoking cessation strategies. Strategies involving psychological motivation and support may be candidates to produce a permanent effect, though short-term evidence has suggested that strength of beliefs about the benefits and harms of smoking are unimportant for quit success [464, 465].

Enthusiasm for projections of behaviour based on survey data should be tempered by caution concerning the limitations and applicability of such data. There is well documented concern about bias and uncertainty surrounding self reports of behaviour [342], though exploration of attrition bias in Chapter 5 highlighted no clear cause for concern in this case study. In addition, survey questions are framed with the aim of minimising bias, and high levels of accuracy from self-reported smoking data have been found elsewhere [466].

There is further issue as to whether it is possible to accurately represent the target population with output from analysis of survey data used here. Though it is possible to set variables in the dynamic behavioural equations with the aim of representing UK smokers likely to receive cessation treatment, data on appropriate values for many variables will not be routinely collected in practice. In lieu of such information, assumptions must be made, as have been here for many variables, including those capturing initial behaviour. However, when assumptions are applied consistently across treatment arms, the importance of such assumptions for incremental results may be small.

Criticism may generally be levelled at the use of survey data instead of trial follow-up data to capture long-run behavioural patterns, but sufficient trial follow-up data

for this purpose, for alcohol and tobacco use at least, appears from Chapters 2, 3 and 4 to be scarce. Such data are needed, and long-run large scale follow-up studies with regular data collection should be actively encouraged. In the meantime, longitudinal individual-level survey data to capture long-run behavioural patterns is available for use.

Given the practical obstacles to estimating dynamic equations in future economic appraisals of competing behaviour change strategies, the consequences of using relatively simple analysis of HILDA data to inform behavioural transition probabilities was tested as part of the sensitivity analysis. Results were similar to baseline in this case, implying that appraisal results based on simple analysis of the appropriate data are a good approximation of results when using dynamic equations estimated using the same data, and could be used in their stead with little consequence. Of course, dynamics and confounding factors not accounted for in simple analysis *could* be important for economic appraisal outcomes in other applications, and this author is cautious about recommending against correct practice. Further, the dynamic equations offer greater flexibility in terms of capturing individual-level characteristics when such data are available and exploration of the importance of these characteristics for cost-effectiveness results. However, when resource limitations mean that undertaking dynamic analysis of appropriate data is not possible, simple analysis of such data may be preferable to simplistic assumptions about long-term behaviour in existing studies which have been at best based on limited trial follow-up data. For future economic appraisals of competing aids for smoking cessation, where data are sufficiently transferable, the mean dynamic equation parameters reported in Table 6 and the accompanying covariance matrix in Table 47 and Table 48 can be utilised.

It is possible that the importance of treatment cost has been understated in the analysis. If an individual relapses to smoking or fails in a quit attempt, they are likely to make assisted attempts again in the future [467]. The BIT model does not explicitly account for future quit attempts, in the manner of the recent simulation model identified in Chapter 3 [214]. However, the HILDA respondents upon whom projections of long-term behaviour are based have been living in a society where aids to smoking cessation have been available in a similar situation to the UK [166,

[424]. Though use of smoking cessation medication is not recorded in HILDA, the propensity to change smoking status after an assisted quit attempt will be captured by observed transitions between behaviour states. The cost of such quit attempts however, is not accounted for. Cheaper treatment options may be more preferable than the BIT model would suggest.

The analysis is subject to the limitations of contributory input data and methods from Chapters 5, 6 and 7, some of which have already been discussed. Aside from these, the data to link smoking status to health was taken from a manufacturer's submission to the STA process and may not represent the best data available [366]. Methods and data to link alcohol use to health were also subject to limitations, and uncertainty around morbidity and mortality rates has not been explored. Despite these limitations, the analysis represents an improvement on what have become standard practice economic appraisals of competing strategies for smoking cessation, and has demonstrated the feasibility and consequences of incorporating dynamic movements in smoking status and their link to alcohol use status in an economic appraisal framework.

8.5. Chapter Summary

The aim of this chapter was to explore the consequences of using dynamic and bivariate behavioural equations to project long-run behavioural patterns within an individual-level health economic simulation model framework. The analyses presented here have demonstrated that cost-effectiveness results for behaviour change intervention comparisons are sensitive to assumptions about the link between short-run observed behaviour and long-run unobserved behaviour. These assumptions should be justified and based on sound analysis of the best available data, which may be longitudinal survey data such as that available from the HILDA survey. Previous analyses using potentially unrealistic assumptions may have overestimated the cost-effectiveness of smoking cessation strategies with high short-term effectiveness [357-367]. However, this chapter has highlighted that if cessation strategies can permanently reduce the propensity to smoke, their value is greatly increased. In the absence of information on this, further important assumptions are necessary.

These issues merit further consideration in the concluding chapter of this thesis. Chapter 9 discusses the findings of this research and the potential implications for future work, including assessment of the merit of the framework for appraisal of behaviour change strategies set out in Chapter 1, in light of the evidence presented on the case study of smoking and alcohol use in the intervening chapters.

9. Chapter 9: Discussion

This thesis has investigated bias in economic evaluations of behaviour change strategies caused by omission of links between behaviours. The investigation focused on the relationship between two behaviours with importance for public health, tobacco use and alcohol use, and the implications for cost-effectiveness estimates of competing interventions to aid smoking cessation. Though there is extensive literature in the area, current knowledge on long-term patterns of tobacco use and alcohol use, and their interrelation, has been shown to be limited. This is reflected in the data and methods used to capture long-term behaviour and its consequences in the numerous economic appraisals in the area to date, which have been potentially inaccurate.

Analysis of alcohol and tobacco use in the HILDA dataset has suggested that use of these substances is both dynamic and interrelated. Analysis of these data provided suitable alternative inputs to potentially more accurately project long-term behaviour in future economic appraisals. Due to the nature of these data, an individual-level simulation modelling framework is necessary to accurately account for long run patterns of behaviour. Appraisal outcomes have been shown to be substantially affected by assumptions about long-run behaviour, and it is possible that reimbursement decisions have been misinformed by inappropriate historical economic appraisals.

9.1. Summary of key contributions, findings and limitations

A key contribution of this thesis is the dynamic, bivariate analysis of tobacco and alcohol use presented in Chapter 5. This contribution to a limited field of evidence may help understanding of the determinants of alcohol and tobacco use, from the importance of addiction, to the influence of person-specific characteristics which are difficult to observe in survey and trial data but should not be ignored. In addition, the results from this analysis were suitable to predict behaviour beyond trial endpoints in an economic evaluation of competing smoking cessation interventions.

The BIT model itself is another sizeable contribution of this thesis. Despite the multitude of economic models to evaluate the cost-effectiveness of competing

smoking cessation strategies published to date, and the appropriateness of an individual-level simulation model type to capture long-run smoking behaviour, the author is aware of only one other individual-level model in the field [214]. This might be explained by a scarcity of long-run follow-up data from smoking cessation trials. Incorporation of dynamic, bivariate equations estimated using large-scale longitudinal data in this thesis to predict long-run behaviour further strengthens the contribution of the BIT model to the field in this context,.

The previous chapter provided a useful insight into the potential mis-estimation of cost-effectiveness results in historical economic evaluations of smoking cessation interventions. If a smoking cessation intervention produces a high 12-month quit rate but does not change time-invariant person-specific characteristics which determine a person's propensity to smoke, their long-run health and healthcare cost benefit may have been exaggerated in past models. If, however, smoking cessation interventions can permanently reduce the propensity to smoke, their benefit for future health and health-care costs may be great. This finding is a further contribution of this thesis to the knowledge base, but ultimately, without knowledge of the relationship between smoking cessation interventions and their influence on these characteristics, the bias in historic economic evaluations with potentially unrealistic assumptions about long-run behaviour is unknown. However, it is likely that the differential effect upon these characteristics between competing drugs to aid cessation attempts is small, and so historic economic evaluations have probably exaggerated the cost-effectiveness of pharmaceutical aids to smoking cessation which have high 12-month cessation rates. This may have led to incorrect resource allocation decisions, potentially including the recommendation of varenicline for smoking cessation in the UK.

A fourth contribution of this work, and a key aim set out in Chapter 1, is evidence on the practicality, feasibility and merit of considering links between behaviours in economic evaluations of behaviour change strategies. This discussion now turns to reflective analysis of the usefulness of the framework for economic evaluations of behaviour change strategies proposed in Chapter 1, in light of the key findings and limitations of each subsequent chapter.

From Figure 1, shown in Chapter 1, which describes the proposed framework, five separable stages to appropriate economic appraisal can be discerned. First, methods and data to perform an economic appraisal without consideration of inter-behavioural links must be established. Second, evidence on links to other health behaviours must be researched, which includes establishing whether past economic appraisals in the area have considered cross-behavioural consequences. Third, data to quantify evidence-supported links to other behaviours need to be either sourced or generated. Fourth, data and methods to connect changes in related behaviours to changes in health, and cost and quality of life outcomes must be established. Fifth, and finally, an analytical tool to accommodate all of these data in order to perform a robust economic appraisal which considers inter-behavioural links must be developed for use, and the analysis run. An overarching aim of subsequent chapters was to test the feasibility and merit of this framework, with a case study focusing on the link between tobacco and alcohol use and its implications for economic appraisal of competing strategies to aid smoking cessation.

Chapter 2 investigated existing evidence on the link between alcohol and tobacco use, thus targeting the second identified stage of the framework. The overriding narrative of the literature is of a complementary relationship between tobacco use and alcohol use, but a relationship that is complex and influenced by confounding factors such as age and gender [76, 79, 82, 91]. Despite the wealth of literature in the area, very little evidence was available on the interaction between alcohol use and tobacco use over time. Exploration of available survey data highlighted a potential lack of data on inter-temporal patterns of alcohol and tobacco use within the same sample, though the HILDA survey was identified as a source of rich longitudinal individual-level data on both alcohol and tobacco use.

The implications from Chapter 2 for wider use of the framework are that while links between behaviours have been the focus of past work and can be useful in determining the importance of inter-behavioural relationships, longitudinal data on linked behaviours may be limited. Without knowledge of patterns of inter-linked behaviours over time, it is not possible to accurately incorporate

consequences of behavioural links into economic appraisals, where long-term health consequences are of great importance.

Chapters 3 and 4 also targeted the second identified stage of the framework, by investigating whether inter-behavioural links have been incorporated into previous economic evaluations of competing strategies for (i) smoking cessation and (ii) alcohol reduction. They have not. These chapters also highlighted data and methods to link behaviour change to long-run health-related consequences, and were thus useful exploring the first and fourth identified stages of the framework. Many economic evaluations studies were identified in chapters 3 and 4, but the overwhelming majority of modelling studies have used cohort model structures and made potentially unrealistic assumptions about long-term behaviour which are not supported by the best available data. Improvements in modelling practice in these areas are merited, aside from consideration of inter-behavioural effects, with a movement towards individual-level models which can handle the complexity of patterns of behaviour over time as well as appropriate analysis of longitudinal data to accurately inform assumptions about long-term behaviour. For future use of the framework, the implications are that economic appraisals of behaviour change strategies are numerous and a search and review of evidence may be cumbersome, but improvements on existing data and methods used will likely be warranted and past incorporation of inter-behavioural effects is unlikely.

Chapter 5 tested the third stage of the framework, by estimating parameters for dynamic equations to quantify the link between smoking status and alcohol use in an economic evaluation model, in the absence of existing data. The parameterised equations are powerful in that they can be used to predict dynamic patterns of behaviour based on nine consecutive years of data from a large sample and flexible in that they control for many important factors which influence smoking and drinking behaviour. Limitations include the potential for bias in self-reported data and the generalisability of Australian general population data to other settings. There are implications from Chapter 5 for future use of the framework, in terms of the practical feasibility of undertaking dynamic and multivariate analysis of survey data in cost-effectiveness projects. The analysis presented in Chapter 5 required a

skill set not typically necessary in economic evaluation projects, and inclusion of such analyses in future economic evaluations may increase the cost of such projects. Further, this case study has considered the case of two inter-related health behaviours; if fully implemented, the framework may warrant analysis of interactions between more than two behaviours. This will be perfectly feasible if the data are available, but would increase the computational burden of estimation, and require programming skills in Stata or alternative software. Nevertheless, dynamic analyses of data on health-related behaviour can contribute substantially to the knowledge base, improving understanding of the complexities and determinants of behaviour, as well as providing useful and flexible evidence for extrapolation of behaviour in cost-effectiveness analyses, as demonstrated here. Efforts to improve understanding of the interrelated dynamics of different health-related behaviours may represent a highly worthwhile use of resources.

Chapter 6 presented results from a standard practice economic appraisal of competing strategies to aid smoking cessation and in doing so established methods and data to perform an economic appraisal without consideration of inter-behavioural links. This was necessary to achieve the first identified stage of the framework for this case study, but the chapter was also useful in providing encouraging evidence on the potential for cytisine as a cost-effective alternative to varenicline for smoking cessation. The economic model was based on a widely used modelling framework, the BENESCO model [363], but the limitations of the analysis were numerous. Paramount among these was the assumption that smokers who fail to successfully quit following treatment at the start of the model, or relapse to smoking following a successful quit, have zero chance of smoking cessation in the future. This is an unrealistic assumption which favours strategies with higher short-term effectiveness. Aside from this, many model parameters were taken from an earlier manufacturer's submission to the NICE appraisal process [366] and may not represent the best available data. Given the depth of research on the economics of smoking, systematically identifying the most appropriate cost, utility and probability parameters to link tobacco use to cost and HRQoL outcomes would be a significant task, though one demanded by NICE guidance [6]. If the framework is to be implemented in future, this would need to

be replicated for each related health behaviour identified as important: a potentially substantial burden.

Chapter 7 established the structure and remaining inputs for the BIT model; Chapter 8 reported results from a re-analysis of the cost-effectiveness of cytisine versus varenicline using this *de novo* individual-level simulation model. Together, these chapters comprise the final identified stage of the framework, in developing and testing an analytical tool to perform a robust economic appraisal which considers inter-behavioural links. There are limitations to the BIT model, including the omission of costs of future NHS-funded smoking cessation attempts, but its structure and key input data represent a clear improvement upon standard practice health economic models in the field. Though the economic appraisal results from Chapter 8 aligned with those of Chapter 6 in that cytisine was shown to be preferable to varenicline for adoption based on current evidence, there were clear differences in incremental outcomes between comparators across the two chapters, driven by different assumptions about long-term behaviour across the BIT and BENESCO models. Cost-effectiveness analyses using modelling structures and assumptions similar to those in the BENESCO model have likely been biased to favour strategies with superior short-term effectiveness. This may have led to misallocation of resources in the past. The risk of resource mis-allocation would be reduced with appropriate assumptions and data used in future models.

There are implications from Chapters 7 and 8 for future use of the framework in terms of the practical feasibility of (i) developing, (ii) populating and (iii) running an individual-level multi-behaviour cost-effectiveness model, which sit alongside the implications from previous chapters. To expand with respect to point (i), the human resources required to build a health economic model are driven by the complexity of the model, which is driven by the complexity of the disease and the availability of data [7]. When multiple behaviours with links to numerous diseases are incorporated into one model, model building will likely be a substantial task. As stated above, data and methods to accurately link behaviour to health-related outcomes are required for every behaviour considered, and these should be identified through a systematic search and review of existing evidence according to NICE guidelines [6]. The resource cost of this may be significant. With respect to

point (iii), due to the scope for increased complexity relative to cohort models, individual-level simulations may be more computationally expensive than cohort analyses, and this has been highlighted in the past as a potential problem for wide use of individual-level simulations for health economic modelling, particularly with respect to undertaking PSA [10]. However, with methodological progress in this area and increases in computing power, this argument is waning [468].

Though difficult to quantify, a valuable lesson from this thesis for similar work in the future is the importance of good communication and understanding within a multidisciplinary team. It is foreseeable, were the framework to be used elsewhere, that skills in econometrics and cost-effectiveness modelling may not be common to any one member of the project team. Care, attention to detail and clear communication across disciplines will be crucial.

Overall, while key findings from this thesis have shown that modelling practice in the field of economic evaluation of behaviour change strategies may require improvement, full implementation of the framework for appraisal proposed in Chapter 1 may not always represent the best use of resources. On the basis of this case study, this author recommends that decisions about the merit of incorporating links between health behaviours into future economic evaluations of behaviour change strategy should be made on a case-by-case basis, perhaps through a scoping exercise to ascertain (i) the potential importance of inter-behavioural links for the appraisal decision (ii) the availability of longitudinal, individual-level data on the behaviours in question. Behavioural links which may have particular importance for appraisal decisions include those in which an improvement in one behaviour leads to a worsening in another behaviour, those in which there is are differential inter-behavioural implications across comparator interventions, and those in which there is high uncertainty around the appraisal decision. The link between smoking and diet may for example be of consequence for economic appraisals of smoking cessation strategies, particularly if one strategy is an appetite suppressant, or if the decision between competing strategies is uncertain.

9.2. Recommendations for future research

There is a clear need for further evidence on long-term patterns of health behaviour. The analysis of HILDA data presented here contributes to evidence on the dynamics of tobacco and alcohol use and their interrelation, but is subject to limitations and would be strengthened by verification through analysis of data from different populations. While further analysis of existing data would be welcome, the availability of such data may be limited. Priority should potentially be given to collecting further data as well as analysing the information that currently exists. Large-scale longitudinal general population surveys with a format similar to HILDA are well suited to this purpose, and the Understanding Society survey in the UK could be a rich source of ongoing information for the UK general population, if the right data were collected [110]. Currently, the survey contains very few questions on alcohol use and detailed information pertaining to weekly consumption for adults only if they are or have been pregnant [110]. Smaller, behaviour-specific studies with regular data collection should also be encouraged, while trials for interventions for behaviour change might be incentivised to collect information on related health behaviour at baseline and follow-up, which will preferably be regular and continue for multiple years in order to capture the dynamics of behaviour.

Dynamic analyses of available longitudinal data on health behaviour are of merit and will hopefully be encouraged, for their important explanatory power, and also as a resource to inform projections of behaviour in cost-effectiveness analyses. Analyses considering networks of behaviour as interrelated outcomes would be of great use, where data are available. Full dissemination of parameter estimates including covariance matrices should be strongly promoted, while analysts who make their estimation code publicly available can not only demonstrate transparency in their work, but help a wider network of researchers with varying skill sets contribute to work in this area.

A move away from cohort state-transition models and towards individual-level simulation models to inform appraisals of competing behaviour change strategies may be merited. This thesis has demonstrated the importance of assumptions about long-term behaviour for economic evaluation outcomes. Potentially

unrealistic assumptions in historical models have at least partly been consequences of inappropriate model structures. Individual-level behaviour is complex and dynamic, and the model structures used, as well as the data to populate them, should ideally reflect this.

9.3. Policy implications

Appraisal of the cost-effectiveness of cytisine as an aid to smoking cessation has shown the drug to have great potential as an alternative to varenicline, currently recommended for use in the UK. The analysis reported in Chapter 6 has contributed to a recommendation for a large-scale trial directly comparing cytisine to varenicline in a sample of UK smokers [368].

Re-estimation of the relative cost-effectiveness of cytisine and varenicline using the BIT model in Chapter 8 did not change the policy recommendations from Chapter 6. However, it has been shown that assumptions in previous analyses using the BENESCO model and other models with similar simplistic assumptions about long-run behaviour may have led to misallocation of resources in the past.

There are further potential policy implications from the dynamic bivariate analysis of tobacco and alcohol use in Chapter 5. Smoking and drinking behaviours are best understood as time-persistent, reinforcing and dynamic behaviours; interventions which target short-term improvements in behaviour may only lead to temporary behavioural improvements. Further research into the time-invariant characteristics which affect the propensity to smoke and drink may aid policy decisions, though these characteristics are inherently difficult to observe.

9.4. Concluding Remarks

Links between health behaviours are potentially of great importance for cost-effectiveness estimates in economic evaluations of competing behaviour change strategies. This thesis has presented an investigation into assumptions about behavioural projections in economic evaluations of smoking cessation strategies. Common assumptions about post-trial behaviour are based on few data and

potentially inaccurate, and have not considered inter-behavioural links. This thesis has provided evidence on the dynamics and interrelation of tobacco and alcohol use in a form that can be used to inform assumptions about behaviour in future cost-effectiveness models, demonstrated potential bias in historical economic evaluations and provided insight into the feasibility and merit of considering links between behaviours in future economic evaluations of behaviour change strategies. The thesis concludes by recommending consideration of the merit of incorporating inter-behavioural links on a case by case basis in economic evaluations; but also with a call for robust and tested assumptions about long-term behaviour in future economic evaluations of behaviour change strategies and for further evidence on the dynamics and interrelation of health-related behaviours to be actively encouraged.

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11. Appendices

11.1. Appendix A: Appendix to Chapter 2

Table 32: Summary of studies analysing links between alcohol use and tobacco use

Lead Author, Year	Study aim	Data, population	Main Statistical Approach	Findings
Correlation between alcohol and tobacco use				
Anthony 2000 [76]	To determine the extent of concurrent use of alcohol and tobacco in the US population	NHSDA and NCS cross-sectional data; General US adult population (n>8,000 NCS; n>17,000 each cross-section of NHSDA, three cross-sections analysed separately)	Analysis of correlation	Patterns of co-occuring use of alcohol and tobacco, with decreasing prevalence after age 25 years
Chiolero 2006 [78]	To assess clustering of risk behaviours (including high alcohol consumption) with level of cigarette consumption	SHS cross-sectional data; General Swiss adult population (n>18,000)	Logistic regression	Odds of multiple risk behaviours higher for smokers than non-smokers and increases with cigarette consumption
Falk 2006 [79]	To update findings of Anthony [76] assessing the extent of concurrent use of alcohol and tobacco in the US	NESARC cross-sectional data; General US adult population (n>42,000)	Analysis of correlation	Tobacco use increases with alcohol consumption; use of both peaks in young adults and decreases

Lead Author, Year	Study aim	Data, population	Main Statistical Approach	Findings
	population			thereafter
Gupta 2005 [80]	To determine the association between concurrent alcohol and tobacco use in an ageing Indian male population	Cross-sectional interview questionnaire of men age >=45 years in Mumbai (n>35,000)	Analysis of correlation	Pattern of co-occurrence, controlling for age, religion and education.
Harrison 2008 [81]	To investigate the association of alcohol use with non-daily smoking in young adults	NESARC cross-sectional data; sub-sample of Wave 1 aged 18-25 years (n>5,500)	Logistic regression	Daily and nondaily smokers more likely to be current drinkers, to drink more alcohol, and to drink more frequently than non-smokers
John 2003 [82]	To investigate associations of different measures of alcohol misuse with tobacco use	TACOS cross sectional data; sub-sample of German smokers (n>2,400)	Logistic regression	Tobacco dependence and being male independent predictors of alcohol dependence
McKee 2007 [98]	To investigate smoking status as a clinical indicator for alcohol misuse	NESARC cross-sectional data; General US adult population (n>42,000)	Logistic regression	Daily and non-daily smokers at heightened risk for hazardous drinking and clinical alcohol misuse, compared to non-smokers
ONS 2012 [85]	To analyse inter-relation	GLS cross-sectional data;	Analysis of	Smokers drink more than

Lead Author, Year	Study aim	Data, population	Main Statistical Approach	Findings
	between alcohol use and tobacco use	General UK adult population (n>16,000)	correlation	non-smokers, but this is driven by never-smokers. Ex-smokers drink nearly as much as smokers
Role of alcohol use in determining tobacco use				
Auguston 2008 [86]	To identify factors associated with smoking cessation	Finnish longitudinal nutritional intervention study with assessment every 4 months for 5 to 8 years; Finnish male smokers aged 50 to 69 years at baseline (n>20,000)	Logistic regression	Smoker who drink over 15g alcohol per day less likely to have a sustained quit as opposed to relapsing than smokers who do not
Breitling 2010 [77]	To examine importance of alcohol consumption for probability of smoking cessation	German cross-section data; German individuals aged 50-74 years presenting for general health screening; sub-sample of 'ever smokers' (n>4,500)	Cox regression	1-99g/week is predictive of smoking cessation, relative to alcohol abstinence
Dawson 2000 [88]	To explore the relationship between drinking and smoking cessation	NLAES two waves of longitudinal data; smoker subsample of	Logistic regression	Smokers who engage in heavy drinking less likely to quit than smokers who

Lead Author, Year	Study aim	Data, population	Main Statistical Approach	Findings
		general US adult population (n>12,500)		do not
Dollar 2009 [56]	To explore importance of own and spousal alcohol and tobacco use for smoking cessation	Prospective study of American couples (n>600)	Cox regression	Drinking >6 drinks or to intoxication 'several times' a month reduces hazard of smoking cessation in married men
Hughes and Callas 2003 [60]	To investigate whether past alcohol problems predict smoking cessation outcomes	American study of smokers randomised to varying strengths of nicotine patch (n>1000)	Logistic regression	Past alcohol problems do not predict smoking cessation outcomes
Hughes 2006 [104]	To investigate whether past alcohol problems predict smoking cessation outcomes using existing evidence	17 articles analysing nicotine dependence between those with and without alcohol problems	Review	Past alcohol problems do not predict smoking cessation outcomes but smokers with current or past alcohol problems are less likely to quit in their lifetime
Hughes and Oliveto 1993 [61]	To investigate alcohol as a predictor of smoking cessation and tobacco withdrawal	Follow-up study Individuals attempting quitting smoking without pharmaceutical aid in America (n>600)	Survival curve analysis	Alcohol use not important in predicting smoking cessation success; cigarette craving levels decreased two weeks after

Lead Author, Year	Study aim	Data, population	Main Statistical Approach	Findings
				cessation for those who did not increase their alcohol intake
Hymowitz 1997 [91]	To identify predictors of smoking cessation in a cohort of smokers followed for 5 years	Telephone survey of American and Canadian cigarette smokers interviewed at baseline and after 5 years (n>13,400)	Logistic regression	Alongside being male, older and having a desire to quit, lower frequency of alcohol intake predicts smoking cessation.
Kahler 2008 [83]	To investigate the role of lifetime alcohol involvement in different smoking decisions such as initiation, progression to daily smoking and then dependence	TTURC: NEFS cross-sectional data; General New England adult population (n>1,600)	Logistic regression	Levels of alcohol involvement increase the risk of ever smoking and progression to daily smoking, but are not important for smoking persistence
Kahler 2009 [92]	To investigate different alcohol use measures as predictors of quitting smoking	ITC-4 two waves of longitudinal data from US, UK, Canadian and Australian adult smokers (n>4800)	Logistic regression	Neither drinking frequency nor weekly quantity of consumption showed robust associations with quitting smoking. Alcohol use measures similar across

Lead Author, Year	Study aim	Data, population	Main Statistical Approach	Findings
				Australia and UK; both bigger users of alcohol than US.
Kahler 2010b [102]	To examine alcohol use and its association with smoking lapses in heavy non-dependent drinkers in smoking cessation treatment	26 week follow-up of American heavy drinking smoking cessation treatment participants (n=236)	Cox regression	Moderate drinking days associated with almost 4 times greater risk of relapse to smoking than non-drinking days
Leeman 2007 [105]	To understand the effect of alcohol upon smoking cessation with and without smoking cessation aids, and the effect of smoking cessation on alcohol use	Data from 149 smoking cessation trials involving nicotine replacement therapy, bupropion or varenicline	Narrative Review	The majority of 11 trials reporting alcohol problem history find no effect. Only two trials that specifically recruited past alcohol dependence patients reported effect of smoking cessation on alcohol use.
Leeman 2008 [66]	To investigate the relationship between smoking cessation treatment failure and current and lifetime alcohol use and problems	Data from an American RCT of two types of motivational interventions both with bupropion for smoking cessation with 12 week follow-up (n=249)	Logistic regression	Probability of smoking highest on heavy drinking days; relapse to smoking slightly more likely for hazardous drinkers than non-hazardous drinkers. Alcohol use disorder

Lead Author, Year	Study aim	Data, population	Main Statistical Approach	Findings
				history did not predict smoking cessation relapse.
McClure 2002 [93]	To examine whether smokers' drinking levels predict smoking abstinence	4 year follow-up study of working smokers in south eastern US (n=728)	Logistic regression	Participants who had quit smoking at follow-up drank less at baseline than continued smokers.
Osler 1999 [95]	To analyse determinants of spontaneous smoking cessation	Longitudinal data on adult smokers in Copenhagen, re-interviewed after 5 and 10-16 years (n>6000)	Logistic regression	High alcohol consumption and being female were independent predictors of non-quitting.
Zimmerman 1990 [84]	To analyse the role of alcohol use in smoking cessation	Cross-section of the Florida adult general population (n>2100)	Logistic regression	Heavy drinkers less likely to have attempted quitting smoking; individuals who enjoy smoking and alcohol concurrently more likely to quit smoking than those who do not use the two concurrently
King 2009 [65]	To investigate alcohol's effect on various aspects of smoking behaviour	Double blind trial of US non-dependent heavy drinking smokers randomised to either alcohol (n=29) or	Analyses of variance	Alcohol, compared with placebo beverage, increased smoking urge, puff count, volume and

Lead Author, Year	Study aim	Data, population	Main Statistical Approach	Findings
		placebo (n=13) beverage		duration in men and women.
McKee 2006 [70]	To examine the role of alcohol use in smoking lapse behaviour	Within-subject trial of US smokers (age 21-55) who drink at least 2 days a week but not alcohol dependent (n=16)	Hypothesis testing (*t* distribution)	After consuming alcohol, subjects less able to resist the first cigarette, initiated smoking sessions sooner and smoked more, compared to placebo beverage.
McKee 2010 [69]	To examine how alcohol alters the subjective effects of smoking in heavy drinking young US adults (age 21-25) who are experimental smokers	Within-subject trial of alcohol's effect on subjective responses to smoking and amount smoked in heavy drinking young US adults (age 21-25) who are experimental smokers (n=19)	Analyses of variance	Expectation of alcohol increased satisfaction and calm with smoking and taste of cigarettes, and alcohol decreased nausea associated with smoking.
Mintz 1985 [71]	To identify a causal link between drinking alcohol and smoking cigarettes	Trial of US narcotic addicts who were smokers and social drinkers, given alcohol and then orange juice in separate sessions (n=14)	Hypothesis testing (*t* distribution)	The hypothesis that alcohol consumption would increase smoking was supported.

Lead Author, Year	Study aim	Data, population	Main Statistical Approach	Findings
Role of tobacco use in determining alcohol use				
Non-alcohol dependent drinkers				
Carmelli 1993 [87]	To investigate the relationship between changes in smoking and drinking over 16 years of adult life	Data from a twin registry on war veterans with 16 year follow-up (n>5500)	Analyses of variance	There was an increase in alcohol consumption in smoking quitters and continuing smokers, but no change in alcohol consumption in continuing non-smokers
Dawson 2012 [97]	To assess correlates of drinking cessation	NESARC two waves of longitudinal data 3 years apart; subsample of participants in both waves consuming alcohol at least once a month in the year before the first wave (n>14850)	Logistic regression	Lifetime smoking cessation associated with increased odds of lifetime drinking cessation across all ages
Gordon 1986 [90]	To examine the relationship between changes in alcohol consumption and other factors	Follow-up study of employed US men 18 years after initial interview (n>850)	Linear regression	There was no association between changes in smoking habits and changes in drinking habits
Kahler 2010a [63]	To examine longitudinally whether quitting smoking is	ITC-4 three waves of annual longitudinal data, from US,	Logistic regression	Low rates of quitting smoking for those who

Lead Author, Year	Study aim	Data, population	Main Statistical Approach	Findings
	associated with decreased alcohol consumption	UK, Canadian and Australian adult smokers (n>3300)		drank heavily more than once a week. Little evidence of sustained smoking cessation changing drinking behaviour.
McKee 2008 [67]	To examine whether nicotine replacement therapy alters alcohol use	Within-subject trial of US smokers (age 21-55) who drink at least 3 days a week but not alcohol dependent (n=19)	Hypothesis testing (*t* distribution)	Nicotine replacement compared to mild nicotine deprivation attenuated subjective and physiological alcohol responses and delayed the initiation of drinking
McKee 2009 [68]	To test whether varenicline reduces alcohol craving and consumption	Double-blind placebo-controlled two-arm trial of non-alcohol dependent US heavy drinkers who smoke (n=20)	Analyses of variance	Varenicline significantly reduced alcohol self-administration in heavy-drinking smokers
Murray 1996 [72]	To test whether changes in smoking are followed by changes in drinking	LHS data on US adult smokers (age 35-60)randomised to either motivational smoking cessation intervention or	Logistic regression	Higher smoking cessation in intervention group but no difference between intervention and control in alcohol use after one

Lead Author, Year	Study aim	Data, population	Main Statistical Approach	Findings
		control (n>5887)		year
Murray 2002 [94]	To assess the evidence that changes in smoking over time are related to changes in drinking or that changes in drinking over time are related to changes in smoking	Two waves of longitudinal data on US adults representative of the general population, about 2 years apart (n=344)	Structural equation modelling	No significant relationships found between changes in smoking and changes in drinking
Alcohol dependent drinkers				
Cosgrove 2011 [108]	To review evidence suggesting nicotine and tobacco smoke modulate the effects of alcohol on neuronal function and implications for recovering alcoholics	Various previous publications	Review	Tobacco smoking during alcohol withdrawal attenuates negative alcohol withdrawal effects
Dawson 2007 [89]	To examine longitudinal changes among individuals recovering from alcohol dependence	NESARC two waves of longitudinal data 3 years apart; subsample in remission from alcohol dependence (n>1750)	Logistic regression	Positive association between baseline smoking and risk of relapse to alcohol, only significant for those who continued smoking across waves
Friend 2005 [57]	To examine the relationship	Sub-sample of smokers in	Kaplan-Meier	Smokers whose cigarette

Lead Author, Year	Study aim	Data, population	Main Statistical Approach	Findings
	between cigarette consumption and alcohol use outcomes over time	US study of interventions for alcohol abuse (n>950)	survival analysis	consumption decreased less likely to relapse to alcohol than those whose consumption increased or remained unchanged
Gulliver 2000 [59]	To investigate the longitudinal relationships between alcohol and tobacco use variables in alcoholics in treatment for alcoholism	6 month follow-up study of US alcoholics in treatment for alcoholism (n=116)	Analysis of variance	Pre-treatment smoking history did not predict post-treatment drinking; the rate of smoking declined following treatment for alcoholism, independent of relapse status
Gulliver 2006 [106]	To review the evidence relating smoking cessation and alcohol abstinence in alcohol dependent and tobacco dependent persons	Various previous publications	Narrative Review	smoking cessation does not disrupt alcohol abstinence and may actually enhance the likelihood of longer-term sobriety
Prochaska 2004 [107]	To assess the effectiveness of smoking cessation interventions for individuals in substance addictions	19 randomised controlled trials of smoking cessation interventions for individuals in substance abuse	Meta-analysis	Smoking cessation interventions provided during addictions treatment associated with

Lead Author, Year	Study aim	Data, population	Main Statistical Approach	Findings
	treatment or recovery	treatment or recovery (n>2000)		increased likelihood of long-term abstinence from alcohol
Schmidt 2001 [74]	To investigate the role of tobacco smoking in the rehabilitation process of alcoholics who smoke	Data from a double-blind placebo-controlled trial of German alcoholics with 12 months follow-up (n=70)	Kaplan-Meier survival analysis	No difference in abstinence rates between smokers and non-smokers, though smokers tended to be abstinent longer than non-smokers
Toneatto 1995 [75]	To investigate the link between alcohol abusers' smoking status when treated for alcohol abuse and patterns of drinking before and after treatment	Data from Canadian alcohol abusers who had received outpatient treatment for alcoholism with 12 months follow-up (n=155)	Analysis of variance	Non-smokers and ex-smokers had more abstinent days than smokers, but smoking groups did not differ at follow-up on other drinking variables
Assessments of validity of concurrent treatment for tobacco and alcohol misuse				
Grant 2007 [58]	To assess bupropion and nicotine patch as smoking cessation aids in alcoholics being treated for their alcoholism	Data from a double blind placebo controlled study of sustained release bupropion as a smoking cessation aid in US alcoholics undergoing treatment for	Hypothesis testing (Chi-squared distribution)	Cessation rates with nicotine patch similar to general population. Alcohol outcomes improved in those who stopped smoking

Lead Author, Year	Study aim	Data, population	Main Statistical Approach	Findings
		their alcoholism, 6 months follow-up (n=58)		
Josephs 2002 [62]	To compare the effectiveness of smoking intervention delivered concurrently with intensive alcohol treatment with smoking intervention that is delayed until 6 months after alcohol treatment	US Alcohol dependence patients who smoke and have desire to quit smoking at some point, nicotine replacement therapy, 18 month follow-up (n>450)	Comparison of percentages	Smoking cessation treatment successful in alcohol treatment patients. Timing of smoking cessation intervention not important for treatment outcomes
Nieva 2010 [73]	To evaluate the effect of intensive tobacco cessation treatment simultaneously with alcohol dependence treatment versus delayed treatment (first alcohol and 6 months later tobacco) upon alcohol and tobacco consumption	Spanish alcohol dependent smokers, being treated for alcohol dependence, randomised between smoking cessation treatment alternatives (simultaneous versus delayed) (n=92)	Survival curves	No differences were in alcohol abstinence rates in time-to-first relapse or in cumulative abstinence at 6 months. Smoking cessation rates were low overall
Kalman 2001 [64]	To assess smoking cessation treatment early in inpatient alcohol treatment versus shortly after an inpatient stay	US smoking patients in a substance abuse treatment program randomised to smoking cessation 2 weeks	Hypothesis testing (*t* distribution and Chi-squared distribution)	Low smoking cessation rates at follow-up. Timing of treatment not important for smoking

Lead Author, Year	Study aim	Data, population	Main Statistical Approach	Findings
		or 6 weeks after admission, 20 weeks follow-up (n=36)		cessation outcome

11.2. Appendix B: Appendix to Chapter 3

Figure 22: Search Strategy, Chapter 3

All searches performed 28th February 2011

Database: HMIC (1979-present), Econlit (1969-present)

1. (zyban or bupropion or wellbutrin or amfebutamone or buproprion).mp. [mp=heading words, abstract, title, country as subject]

2. nicotine replacement therap*.mp. [mp=heading words, abstract, title, country as subject]

3. (nicotine adj3 (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*)).mp. [mp=heading words, abstract, title, country as subject]

4. 1 or 2 or 3

5. (cost* or econom* or pharmacoeconom* or price* or pricing).mp. [mp=heading words, abstract, title, country as subject]

6. 4 and 5

Database: NHS EED

1. zyban or bupropion or wellbutrin or amfebutamone or buproprion

2. nicotine (w) replacement (w) therap$ or nrt

3. nicotine (3w) (patch$ or gum or inhaler$ or spray$ or tablet$ or transdermal or lozenge$)

4. 1 or 2 or 3

Database: HTA

1. zyban or bupropion or wellbutrin or amfebutamone or buproprion

2. cost$ or econom$ or pharmacoeconom$ or price$ or pricing

3. nicotine

4. 2 and 3

5. 1 or 4

Database: MEDLINE

1. Economics/

2. exp "Costs and Cost analysis"/

3. "Value of Life"/

4. Economics, Dental/

5. exp Economics, Hospital/

6. Economics, Medical/

7. Economics, Nursing/

8. Economics, Pharmaceutical/

9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.

11. (expenditure$ not energy).ti,ab.

12. (value adj1 money).ti,ab.

13. budget$.ti,ab.

14. 10 or 11 or 12 or 13

15. 9 or 14

16. letter.pt.

17. editorial.pt.

18. historical article.pt.

19. 16 or 17 or 18

20. 15 not 19

21. Animals/

22. Humans/

23. 21 not (21 and 22)

24. 20 not 23

25. (metabolic adj cost).ti,ab.

26. ((energy or oxygen) adj cost).ti,ab.

27. 24 not (25 and 26)

28. zyban or bupropion or wellbutrin or amfebutamone or buproprion

29. nicotine replacement therap*

30. (nicotine adj3 (patch* or gum or inhaler* or spray* or tablet* or transdermal or lozenge*))

31. 28 or 29 or 30

32. 27 and 31

Table 33: Data Extraction Table, Chapter 3

Study 1st Author and Year: **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
Modelling Studies					
Akehurst 1994a	UK; *Not clear;* **CEA**	Healthcare Payer; 36 years; General population of adult smokers	12 month cessation rate; Cost/LY gained; *0%*	1. GP BA [3.7%] **2. GP BA + NRT patch [11.7%]**	Intervention cost; *No clearly reported assumption about number of quit attempts*
Akehurst 1994b	UK; *Not clear;* **CEA**	Healthcare Payer; 36 years; Heavy adult smokers (>22 cigarettes per day)	Cessation rate (length of abstinence or from intervention unclear); Cost/LY gained; *0%*	1. GP BA [3.7%] **2. GP BA + NRT spray [26.0%]**	Intervention cost, SRDMC; *Intervention impacts remain continuous as people enter and*

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
					leave the model
Annemans 2009	Belgium; *Pfizer;* **CUA**	Healthcare Payer; Lifetime; General population of adult smokers	12 month continuous cessation rate; Cost/QALY gained; *6.8% annually years 1 to <6, 2% annually years 6 to <10, 1% annually years 10 onwards*	1. Self Quit [5.0%] 2. BC [9.4%] 3. BC + NRT [14.8%] 4. BC + Bupropion (12 weeks) [15.4%] **5. BC + Varenicline [22.5%]**	Intervention cost, SRDMC; *Single quit attempt at the start of the model*
Bae 2009	South Korea; *Pfizer;* **CUA**	Societal; Lifetime; Adult smokers with a desire to quit	Cessation rate (length of abstinence or from intervention unclear); Cost/QALYs gained; *6.8% annually years 1 to <6, 2% annually years 6 to <10, 1% annually years 10 onwards*	1. Willpower [10.6%] 2. NRT [17.2%] 3. Bupropion [17.8%] **4. Varenicline [25.2%]**	Intervention cost, SRDMC; *No clearly reported assumption about number of quit attempts*
Bauld 2011	UK;	Healthcare Payer;	12 months	1. Self Quit [1.5%]	Intervention

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
	Glasgow Centre for Population Health, NHS Greater Glasgow and Clyde and NHS Health Scotland; **CUA**	Lifetime; Smokers aged 16 years and over with a desire to quit	continuous cessation rate, **biochemically confirmed**; Cost/QALY gained; *24% years 1 to <3, 10% years 3 to <5, 2% years 5to <8, 0% onwards*	2. Pharmacy-based BC + NRT [2.5%] 3. GC + NRT + pharmacy follow up [5.5%]	cost (including overhead cost); *Single quit attempt at the start of the model*
Bertram 2007	Australia; *Australian National Health and Medical Research Council (NHMRC);* **CUA**	Healthcare Payer; Lifetime; Adult smokers with a desire to quit	12 month cessation rate (ORs); Cost/DALY gained; *10-48% annually years 1 to 4; 0% year 5 onwards*	1. Self Quit [8.6%] 2. NRT [OR: 1.73] 3. Bupropion [OR: 2.54] 4.Bupropion [OR: 2.54], followed by NRT at 12 months if Bupropion not successful [OR: 1.73]	Intervention cost, SRDMC; *No clearly reported assumption about number of quit attempts*
Bolin 2006	Sweden; *GlaxoSmithKline;* **CUA**	Societal; 20 years; General population of	12 month continuous cessation rate; Cost/QALY gained; *35% over time*	1. NRT patch + MS [15.0%]; 2. NRT gum + MS [15.6%]; 3. Bupropion + MS [18.9%]	Intervention cost, SRDMC *30% of smokers*

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
		adult smokers	*horizon*		*attempt to quit each year*
Bolin 2008	Sweden; *Pfizer;* **CUA**	Societal; Lifetime; Adult smokers with a desire to quit	12 month continuous cessation rate; Cost/QALY gained *6% annually years 1 to <6,* *2% annually years 6 to <10, 1% annually years 10 onwards*	1. MS + Bupropion [15.7%] **2. Optional MS + Varenicline [22.5%]**	Intervention cost, SRDMC; *Single quit attempt at the start of the model*
Bolin 2009	Sweden; *Pfizer;* **CUA**	Healthcare Payer; Societal; Lifetime; Adult smokers with a desire to quit	12 month continuous cessation rate; Cost/QALY gained; *6% annually years 1 to <6,* *2% annually years 6 to <10, 1% annually years 10 onwards*	1. MS + Varenicline + Placebo (additional 12 weeks) if abstinent at 12 weeks [23.2%] **2. MS + Varenicline + Varenicline (additional 12 weeks) if abstinent at 12 weeks [27.4%]**	Intervention cost, SRDMC; *Single quit attempt at the start of the model*
Bolin 2009a	Sweden, UK, France, Belgium;	Healthcare Payer; Lifetime;	12 month continuous cessation rate;	1. NRT patch [20.3%] **2. Varenicline [26.1%]**	Intervention cost, SRDMC;

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
	Pfizer; **CUA**	General population of adult smokers	Cost/QALY gained; *Considered but not reported in the text*		*Single quit attempt for 25% of smokers at the start of the model.*
Cornuz 2003	Switzerland; *Swiss Federal Office for Public Health;* **CEA**	Healthcare Payer; Lifetime; Dependent adult smokers (average 20 cigarettes per day)	12 month cessation rate (ORs); Cost/LY saved; *35% over time horizon*	1. GP BC [OR*:1.73] 2. GP BC + NRT gum [OR**:1.63] 3. GP BC + NRT patch [OR**:1.79] 4. GP BC + NRT spray [OR**:2.35] 5. GP BC + NRT inhaler [OR**:2.14] 6. GP BC + Bupropion [OR**:2.30]	Intervention cost; *25% of current smokers are in the preparation stage for quitting;* *No reported assumption about number of quit attempts*
Cornuz 2006	Switzerland, Canada, France, Spain, USA, UK;	Healthcare Payer; Lifetime; Dependent adult	12 month point prevalence cessation rate (ORs);	1. GP BC [OR*:1.73] 2. GP BC + NRT gum [OR**:1.66]	Intervention cost;

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
	Not clear; **CEA**	smokers (average 20 cigarettes per day)	Cost/LY gained; *35% over time horizon*	3. GP BC + NRT patch [OR**:1.80] 4. GP BC + NRT spray [OR**:2.35] 5. GP BC + NRT inhaler [OR**:2.14] 6. GP BC + Bupropion [OR**:2.51]	*25% of current smokers are in the preparation stage for quitting;* *No reported assumption about number of quit attempts*
Cromwell 1997	USA; *US Department of Health and Human Services (HHS);* **CUA**	Healthcare Payer; Not explicitly reported; General population of adult smokers	5 months minimum cessation rate; Cost/QALY saved; *45% over time horizon*	1. Self quit [5%] 2. BA [5.9%] 3. BA + NRT patch [11.7%] 4. BA + NRT gum [8.7%] 5. Brief BC [6.9%] 6. Brief BC + NRT patch [13.4%] 7. Brief BC + NRT gum [10.0%] 8. BC [11.2%] 9. BC +NRT patch [21.0%] 10. BC + NRT gum [15.9]	Intervention cost (includes cost of motivating unwilling smokers to quit); *Single quit attempt for 75% of smokers at the start of the*

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
				11. Intense BC [11.6%] 12. Intense BC + NRT patch [21.6%] 13. Intense BC + NRT gum [16.5%]	*model*
Feenstra 2005	The Netherlands; *Dutch Public-Private Partnership to reduce tobacco dependence;* **CUA**	Healthcare Payer; Lifetime; Smokers aged 10 years and older	12 month continuous cessation rate; Cost/QALY gained; *Considered, but values not fully reported in text*	1. Willpower (with access to the interventions below, using uptake rates) [3.4%] 2. GP BA [7.9%] 3. GP BA + NRT [12.7%] 4. BC + NRT [15.1%] 5. BC + Bupropion [17.2%] 6. TC [7.6%]	Intervention cost; *Interventions for 25% of smokers each year*
Fiscella 1996	USA; *Not clear;* **CUA**	Healthcare Payer; Not explicitly reported; Adult smokers receiving primary care	12 month cessation rate, **biochemically validated**; Cost/QALY saved; *35% over time horizon*	1. Self quit [2.5%] 2. GP BC [4.0%] **3. GP BC + NRT patch [7.9%]**	Intervention cost; *Single intervention at the start of the model*

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
Flack 2007	UK; *NICE Rapid Reviews;* **CUA**	Healthcare Payer; Lifetime; General population of smokers aged 16 years and older	12 month cessation rates; Cost/QALY gained; *35% over time horizon*	1. Self quit [2.0%] 2. GP BA [3.0%] 3. GP BA + SHM [4.0%] 4. BA + SHM + NRT [6.0%] 5. BA + SHM + NRT + Specialist Clinic [15.0%] 6. Brief BC + Bupropion [24.0%] **7. BC + Bupropion [31.0%]** 8. NRT patch [12.0%] 9. GC + NRT patch [21.0%] 10. BC + NRT patch [16.0%] 11. Pharmacist Consultation + NRT patch [24.0%] 12. BC + Pharmacist Consultation + NRT patch [35.0%]	Intervention cost, SRDMC; *Single quit attempt at the start of the model; underlying quit rate*
Gilbert 2004	The Seychelles; *Not clear;* **CEA**	Healthcare Payer; Lifetime; General population of	12 month continuous cessation rate (ORs); Cost/LY gained; *35% over time*	1. BC [OR*:1.73] 2. BC + NRT gum (3 months) [OR**:1.66] 3. BC + NRT patch (3	Intervention cost; *25% of current*

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
		adult smokers	*horizon*	months) [OR**:1.80] 4. BC + NRT spray (3 months) [OR**:2.35] 5. BC + NRT inhaler (3 months) [OR**:2.14] 6. BC + Bupropion (3 months) [OR**:2.51]	*smokers prepared to make a quit attempt;* *No reported assumption about number of quit attempts*
Godfrey 2005	UK; *DoH Policy Research Programme;* **CEA**	Healthcare Payer; Lifetime; Adult smokers with a desire to quit	4 week cessation rate, **biochemically confirmed**; Cost/LY gained; *65% from 4 weeks to 52 weeks, 54% from 52 weeks to 8 years*	1. Background cessation [2.0%] **2. Specialist smoking cessation services [13.56%]**	Intervention cost (including overhead cost), SRDMC; *Background quit rate 2%*
Halpern 2000*	USA; *Glaxo Wellcome;* **CBA**	Healthcare Payer, Insurers, Employers; Lifetime; General	12 month cessation rate; Benefit-to-cost ratio; *Considered, but values not reported in*	1. Bupropion 2. Bupropion + BA 3. Bupropion + BC 4. Bupropion + NRT patch 5. Bupropion + BA + NRT	Intervention cost, cost of a smoking employee (including

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
		population	*text*	patch 6. Bupropion + BC + NRT patch 7. NRT patch 8. NRT patch + BA 9. NRT patch + BC 10. BA 11. BC 12. Self Quit	productivity cost and SRDMC); *34% of smokers attempt to quit each year*
Halpern 2007	USA; *Pfizer*; **CEA/CBA**	Healthcare Payer; Employers; 10 years; General population	12 month continuous cessation rate; Cost per additional quitter; *14% 1 to <2 years, 10.3% 2 to <3 years, 3.4% 3 to <4 years; 3.0% 4 to <5 years; 1.5% 5 to <11 years; 0% 11 years onwards*	1. Self Quit [3.2%] 2. BC + NRT patch [9.8%] 3. BC + Bupropion [15.5%] **4. BC + Varenicline [22.5%]**	Intervention cost, Future general medical costs; *43% of smokers attempt to quit each year, but the intervention was only available in the first year*

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
Heitjan 2008	USA; *National Cancer Institute and National Institute on Drug Abuse; GlaxoSmithKline;* **CEA**	Healthcare Payer; Lifetime; General population of adult smokers	6 month minimum continuous cessation rate; Cost/LY gained; *50% across time horizon for temporary quitters (temporary quitters comprise 40% of total quitters)*	1. Self Quit [5.0% at 12 months] 2. BC + NRT patch [23.0% at 6 months] 3. BC + Bupropion [17.0% at 6 months] **4. Varenicline [35% at 12 months]** 5. Test for genotype; assign either to Bupropion [27.0% at 6 months] or NRT patch [19.0% at 6 months]	Intervention cost; *50% attempt to quit each year*
Hind 2009	UK; *NIHR HTA Programme;* **CUA**	Healthcare Payer; Lifetime; Adult smokers with a desire to quit	12 month continuous cessation rate; Cost/QALY gained; *6.3% annually years 1 to <6, 2% annually years 6 to <10, 1% annually years 10 onwards*	1. Placebo [9.4%] 2. NRT [14.9%] 3. Bupropion [15.5%] **4. Varenicline [22.5%]**	Intervention cost, SRDMC; *Single quit attempt at the start of the model*
Hoogendoorn	The	Healthcare Payer;	12 month cessation	1. Self Quit [5.0%]	Intervention

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
2008	Netherlands; *Pfizer;* **CUA**	Lifetime; General population of adult smokers	rate; Cost/QALY gained; *6.8% years 1 to <6, 0% years 6 onwards*	2. NRT (type weighted by use) [14.8%] 3. Nortriptyline [17.0%] **4. Varenicline [22.4%]**	cost, SRDMC; *Single quit attempt for 25% of smokers at the start of the model*
Howard 2008	USA; *Pfizer;* **CUA**	Healthcare Payer; Lifetime; General population of adult smokers	12 month cessation rate, **biochemically confirmed**; Cost/QALY gained; *6.3% annually years 1 to <6, 2% annually years 6 to <11, 1% annually years 10 onwards*	1. Self Quit [5%] 2. NRT (type weighted by use) [15.4%] 3. Bupropion (12 weeks) [15.4%] **4. Varenicline [22.4%]**	Intervention cost, SRDMC; *Single quit attempt for 25% of smokers at the start of the model*
Igarashi 2009	Japan; *Pfizer;* **CUA**	Healthcare Payer; Lifetime; General population of	12 month continuous cessation rate, **biochemically confirmed**;	1. BC + Placebo [men 25.5%; women 16.1%] **2. BC + Varenicline [men 37.9%; women 22.2%]**	Intervention cost, administration cost;

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
		smokers that started smoking at age 20 years	Cost/QALY gained; *Not considered*		*Single intervention at the start of the model*
Javitz 2004	USA; *National Cancer Institute;* **CBA**	Employer; 5 years; Adult smokers with a desire to quit	Self-reported 7 day point prevalence cessation rate at 12 months; Net monetary benefit; Not considered	1. Proactive TC + Bupropion [20.4%] 2. SHM + Bupropion [12.6%] 3. Proactive TC + High Dose Bupropion [22.2%] 4. SHM + High Dose Bupropion [14.7%]	Intervention cost; *Employees entered the program on a continuing basis*
Javitz 2004a	USA; *National Cancer Institute;* **CUA**	Healthcare Payer; Lifetime; Adult smokers with a desire to quit	Self-reported 7 day point prevalence cessation rate at 12 months; Cost/QALY saved; *37% over time period*	1. Proactive TC + Bupropion [20.4%] 2. SHM + Bupropion [12.6%] 3. Proactive TC + High Dose Bupropion [22.2%] 4. SHM + High Dose Bupropion [14.7%]	Intervention cost; *Single intervention in first year of the model*
Kaper 2006	The	Societal;	7 day point	**1. Reimbursement for**	Intervention

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
	Netherlands; *STIVORO (Dutch smoking cessation foundation) and the Dutch Asthma Foundation;* **CUA**	Lifetime; General population of adult smokers	prevalence abstinence at 12 months, **biochemically confirmed**; Cost/QALY gained; *25% lifetime relapse*	**NRT, bupropion and BC for 6 months [5.5%]** 2. No reimbursement [2.8%]	cost (including overhead cost), travel costs, productivity losses; *No reported assumption about number of quit attempts*
Knight 2010	USA; *Pfizer;* **CUA**	Healthcare Payer; Lifetime; Adult smokers with a desire to quit	12 month continuous cessation rate; Cost/QALY gained; *0%*	1. Self Quit [5.0%] 2. Placebo [9.3%] 3. NRT [15.4%] 4. Bupropion [15.9%] 5. Varenicline [22.9%] **6. Varenicline + second course or Varenicline if abstinent at 12 weeks [27.7%]**	Intervention cost, SRDMC; *Single quit attempt at the start of the model*
Levy 2002	USA; *US HHS; Robert*	Insurer; 1 year;	12 month cessation rate;	1. No coverage [4.5%] 2. Prescription NRT +	Intervention cost;

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
	Johnson Wood Foundation; **CEA**	General population of adult smokers	Cost/quitter; N/A	Bupropion [10.7%**] 3. Prescription NRT + Bupropion + OTC NRT [16.9%**] 4. BC [5.9%**] 5. BC + Prescription NRT + Bupropion [17.9%**] 6. BC, Prescription NRT, Bupropion, OTC NRT, alone or in conjunction [28.6%**]	*No more than 2 quit attempts in a year;* *45% of smokers attempt to quit*
Levy 2006	USA; *National Institutes of Health;* **CBA**	Employer; Insurer; 20 years; General population	Cessation rate (length of abstinence or from intervention unclear); Benefit-to-cost ratio; *20% annually years 0 to <2 after quitting, 2% annually years 2 to <5 after quitting, 1% annually years 5*	1. No smoking cessation coverage program [4.3%] **2. Smoking cessation coverage program [5.9-28.6% **]**	Intervention cost, Future general medical expenditure; *Every year there was a chance current smokers would quit*

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
			after quitting onwards		
Linden 2010	Finland; *Pfizer;* **CUA**	Healthcare Payer; Lifetime; Adult smokers with a desire to quit	12 month continuous cessation rate, **biochemically confirmed**; Cost/QALY gained; *6% annually years 1 to <6, 2% annually years 6 to <10, 1% annually years 10 onwards*	1. Self quit [5.0%] 2. Bupropion [15.7%] **3. Varenicline [22.5%]**	Intervention cost, SRDMC; *Single quit attempt at the start of the model*
McGhan 1996	USA; *Lederle Laboratories;* **CBA**	Employer; 1 year; Smoking employees	6 month minimum cessation rate; Net monetary benefit; *N/A*	1. Self Quit + SHM [15.0%] 2. Intense BC [26.0%] 3. Brief BC + NRT patch [15.0%] 4. Intense BC + NRT patch [20.0%] 5. Group BC + NRT patch [26.0%]	Intervention cost, cost of a smoking employee (including productivity cost), Future general medical

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
				6. Pharmacist Consultation + NRT patch [31.0%] **7. Pharmacist Consultation + Intense BC + NRT patch [44.0%]**	costs; *Single intervention at the start of the model*
Nielsen 2000	USA; *Glaxo Wellcome;* **CBA**	Employer; 1 year; Population of adult smokers (socio-demographic and mean smoking rate figures reported)	12 month point prevalence cessation rate, **biochemically confirmed**; Net monetary benefit; *Not considered*	1. Placebo [15.6%] **2. Bupropion [30.3%]** 3. NRT patch [16.4%] 4. NRT patch + Bupropion [35.5%]	Intervention cost, cost of a smoking employee (including productivity cost); *Single intervention at the start of the time horizon*
Ong 2005	USA; *National Cancer Institute; Health*	Healthcare Payer; Lifetime; Dependent adult	6 month continuous cessation rate; Cost/QALY gained;	1. Self Quit [10.6%] **2. OTC NRT gum or patch [7.5%**]**	Intervention cost;

Study 1st Author and Year; **Study Quality**	**Country; Sponsorship; Study Design**	**Study perspective; Time Horizon; Study population**	**Effectiveness measure; Main outcome measure; *Relapse Rate***	**Alternatives [Effectiveness Rates] Optimal Alternative Highlighted**	**Resources; *Key Assumptions***
	Resources and Services Administration; **CUA**	smokers (>14 cigarettes per day)	*35% over time horizon*		*64% of smokers ready for attempt to quit ; No more than 2 quit attempts in the first year and all failed quitters would try NRT again; No clearly reported assumption about number of quit attempts in the long run*
Orme 2001	UK; *Glaxo Wellcome;* **CEA**	Healthcare Payer; 20 years; General population of adult smokers	Cessation rate (length of abstinence or from intervention unclear); Cost/LY gained;	1. Willpower [1.0%] 2. GP BA [3.0%] 3. Group Therapy [9.0%] 4. NRT or Bupropion [13.0%]	Intervention cost, SRDMC; *Interventions only available in*

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
			6.9% annually at 1 year, falling by 1% increments to 0% (timing or increments not reported)		*first year of the model*
Oster 1986	USA; *Merrel Dow Pharmaceuticals; National Institutes of Health;* **CEA**	Healthcare Payer; Lifetime; Adult smokers receiving primary care	12 month cessation rate; Cost/LY gained; *0%*	1. GP BA [4.5%] **2. GP BA + NRT gum [6.1%]**	Intervention cost; *Single intervention at the start of the model*
Parrott 1998	UK; *UK Health Education Authority;* **CEA**	Healthcare Payer, Societal; 43 years; General population	6 month minimum cessation rate; Cost/LY gained; *Not considered*	1. Self Quit [1.0%] 2. BA + Willpower [3.0%] 3. BA + SHM [4.0%] 4. BA + NRT [6.0%] 5. Smokers' clinic + NRT [20%]	Intervention cost (including training cost); *40% of those advised to cease made a quit attempt each year*

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
Shanahan 2003	Australia; *Not clear;* **CEA**	Healthcare Payer; 1 year; General population of adult smokers	12 month cessation rate; Narrative comparison of relative costs and effectiveness; *N/A*	1. OTC NRT patch [Not reported] 2. GP BC + NRT patch [14.0-21.0%] 3. GP BA + Bupropion [21.0-35.0%]	Intervention cost; *No clearly reported assumption about number of quit attempts*
Shearer 2006	Australia; *Australian Government Department of Health and Ageing;* **CEA**	Healthcare Payer; 6 months; General population of adult smokers	6 month continuous cessation rate; Cost/additional quitter; *N/A*	1. BA + SHM [6.0%] **2. TC + SHM [9.0%]** 3. TC + SHM + NRT patch [17.0%] 4. Proactive TC + SHM + NRT patch [27.0%] 5. TC + SHM + Bupropion [19.0%] 6. Proactive TC + SHM + Bupropion [32.0%] 7. TC + SHM + NRT patch + Bupropion [19.0%]	Intervention cost; *No clearly reported assumption about number of quit attempts*

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
Song 2002	UK; *Not clear, but based on study funded by NHS R&D HTA Programme;* **CUA**	Healthcare Payer; Lifetime; General population of adult smokers	12 month continuous cessation rate; Cost/QALY gained; *40% over time horizon*	1. BC [10.0%] or BA [4.0%] 2. BC or BA + NRT [OR: 1.67] 3. BC or BA + Bupropion [OR: 2.1] 4. BC or BA + NRT + Bupropion [OR: 2.8] (ORs all versus placebo)	Intervention cost; *Single quit attempt at the start of the model; underlying quit rate*
Stapleton 1999	UK; *MRC; Pharmacia and Upjohn;* **CEA**	Healthcare Payer; Not explicitly reported; Dependent adult smokers (>13 cigarettes per day) with a desire to quit	12 month cessation rate, **biochemically confirmed;** Cost/LY saved; *40% over time horizon*	1. GP BA [4.5%] **2 GP BA + NRT patch [9.6%]**	Intervention cost; *Single intervention at the start of the model*
Thavorn 2008	Thailand; *Thailand Research Fund & Thai Pharmacy*	Healthcare Payer; Lifetime; Adult smokers that regularly	12 month continuous cessation rate; Cost/LY gained; *Not considered*	1. Dependence and motivation discussion, BA, provision of therapy [2.7%] **2. Community cessation**	Intervention cost, SRDMC; *Single*

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
	Network for Tobacco Control **CEA**	smoke 10 to 20 cigarettes per day		**program with Dependence and motivation discussion, BA, provision of appropriate therapy with SHM, follow up care [14.3%]**	*intervention over the time horizon*
Tran 2010	Canada; *Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Prince Edward*	Healthcare Payer; Lifetime; Adult smokers with a desire to quit	12 month continuous cessation rate, **biochemically confirmed**; Cost/QALY gained; *8.7% annually years 1 to <6, 3.8% annually years 6 to <8, 2.1% annually years 8 to <11, 0.5% annually year 11 onwards*	1. Self Quit [3.4%] 2. NRT patch [5.9%] 3. NRT gum [5.6%] 4. NRT inhaler [7.3%] 5. NRT lozenge [7.5%] 6. Bupropion [6.4%] **7. Varenicline [8.8%]**	Intervention cost, SRDMC; *Single intervention at the start of the model*

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
	Island, Saskatchewan, and Yukon; **CUA**				
Vemer 2010	The Netherlands, Germany, Sweden, UK, Belgium, France; *Pfizer;* **CUA**	Healthcare Payer; Lifetime; General population of adult smokers	12 month continuous cessation rate; Cost/QALY gained; *Considered but not reported*	1. Self Quit [5.0%] 2. BC + NRT [14.8%] 3. BC + Bupropion [17.0%] **4. BC + Varenicline [22.4%]**	Intervention cost, SRDMC *Single quit attempt for 25% of smokers at the start of the model*
Wang 2008	UK; *NHS R&D HTA Programme;* **CUA**	Healthcare Payer; Lifetime; Current UK smokers (targeting those unwilling or unable to make an abrupt attempt to quit)	12 month minimum continuous cessation rate; Cost/QALY gained; *30% over time horizon*	1. CDTQ: NRT OTC [2.2%] 2. CDTQ: NRT prescription [2.0%] 3. CDTQ: NRT prescription + BC or GBC [5.3%] 4. NRT OTC [6.6%] 5. NRT prescription [5.9%] 6. NRT prescription + BC or GBC [16.0%]	Intervention cost; *Single quit attempt*

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
				7. Self Quit [4.0%]	
Warner 2004	USA; *Robert Wood Johnson Foundation;* **CEA/CBA**	Insurer; Societal; 30 years; Lifetime General population	Lifetime cessation rate; Cost/LY gained; Net monetary benefit; *Not considered*	1. Self Quit; 2. Smoking cessation services [15%****]	Intervention cost, Future general medical expenditure, Membership premium (CBA only); *Each year the model gives a smoker a chance of quitting*
Wasley 1997	USA; *Merrel Dow Pharmaceuticals;* **CEA**	Healthcare Payer; Not explicitly reported; Heavy adult smokers (>19 cigarettes per day) receiving	12 month cessation rate; Cost/LY gained; *35% over time horizon*	1. GP BA [4.5%] **2. GP BA + NRT patch [17.6%]**	Intervention cost; *Single intervention at the start of the model*

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
		primary care			
Welton 2008	UK; *Medical Research Council;* **CUA**	Healthcare Payer; Lifetime; Adult smokers with a desire to quit	12 month cessation rate; Cost/QALY gained (Incremental Net Benefit); *Beta distribution (38,57)*	1. BA [5.1%] 2. NRT [19%] 3. Bupropion [21%] **4. NRT + Bupropion [27%]** 5. BA for CC genotype [5.1%], NRT for CT and TT genotypes [21%] 6. BA for CC genotype [5.1%], Bupropion for CT and TT genotypes [17%] 7. NRT for CC genotype [18%] or BA for CT and TT genotypes [5.1%] 8. NRT for CC genotype [18%] or Bupropion for CT and TT genotypes [17%] 9. Bupropion for CC genotype [24%] or BA for CT and TT genotypes [5.1%] 10. Bupropion for CC	Intervention cost; *No clearly reported assumption about number of quit attempts*

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
				genotype [24%] or NRT for CT and TT genotypes [21%]	
Woolacott 2002	UK; *NHS R&D HTA Programme;* **CUA**	Healthcare Payer; Lifetime; General population of smokers	12 month continuous cessation rate; Cost/QALY saved; *40% over time horizon*	1. MS or BC [4.0%]; 2. NRT + MS [6.5%]; 3. Bupropion + MS [8.1%]; 4. Bupropion + NRT + MS [9.9%]	Intervention cost; *30% of smokers attempt to quit and can only use one intervention;* *Background quit rate 1%*
Primary Studies					
An 2006	USA; *Not clear;* **CEA**	Healthcare Payer; 6 months; Adult smokers (consuming >4 cigarettes per day) with a desire	Self-reported 30 day point prevalence cessation rate at 6 months; Cost/quit; *N/A*	1. Cessation service without pharmacology [10.0%] 2. Cessation service + NRT patch or gum [18.2%]	Intervention cost; *Single intervention at the start of the*

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
		to quit			*time horizon*
Boyd 2009	UK; *Glasgow Centre for Population Health, NHS Greater Glasgow and Clyde and NHS Health Scotland;* **CEA**	Healthcare Payer; 4 weeks; Smokers aged 16 years and over with a desire to quit	4 week cessation rate, **biochemically confirmed**; Cost/additional quitter; *N/A*	1. Self Quit (10.0%) 2. Pharmacy support + NRT [17.0%] 3. GC + NRT + pharmacy follow up [31.0%]	Intervention cost (including overhead costs); *Single intervention at the start of the time horizon*
Hall 2005	USA; *US HHS;* **CEA**	Healthcare Payer; 12 months; Adult smokers with a desire to quit and willingness to participate in a clinical trial	12 month cessation rates, **biochemically confirmed**; Average cost/12 month cessation rate; *N/A*	1. BA + SHM [13%] 2. BA + SHM + Nortriptyline [23%] 3. BA + SHM + Bupropion [29%] 4. BA + SHM + GC [21%]	Intervention cost (including overhead costs); *Single intervention at the start of the time horizon*
Halpin 2006	USA;	Insurers;	Self-reported 7 day	1. Bupropion (12 weeks) or	Intervention

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
	California Tobacco-Related Disease Program; **CEA**	8 months; Insured adult smokers (at least 1 cigarette in last 7 days) willing to participate in a clinical trial	point prevalence cessation rate at 8 months; Costs and cessation rates reported separately; *N/A*	NRT (patch, inhaler, or nasal spray) [19%] 2. Proactive TC + Bupropion (12 weeks) or NRT (patch, inhaler, or nasal spray) [13%] 3. Proactive TC + Bupropion (12 weeks) or NRT (patch, inhaler, or nasal spray) if participant enrolled in the TC [18%]	cost; *Single intervention at the start of the time horizon*
Hollis 2007	USA; *National Cancer Institute;* *GlaxoSmithKline;* **CEA**	Healthcare Payer; 1 year; Adult smokers (consuming >4 cigarettes per day) with a desire to quit	30 day point prevalence cessation rate at 12 months; Cost/Quit; *N/A*	1. Brief TC [11.7%] 2. TC [13.8%] 3. Intense TC [14.3%] 4. Brief TC + NRT patch [17.1%] 5. TC + NRT patch [20.1%] 6. Intense TC + NRT patch [21.2%]	Intervention cost (including training cost); *Single intervention at the start of the time horizon*
Jackson 2007	USA; *Pfizer;*	Employer; 1 year;	12 month continuous cessation rates,	1. Brief BC + Placebo [8.4%] 2. Brief BC + Bupropion (12	Intervention cost, cost of a

Study 1st Author and Year; **Study Quality**	**Country; Sponsorship; Study Design**	**Study perspective; Time Horizon; Study population**	**Effectiveness measure; Main outcome measure; *Relapse Rate***	**Alternatives [Effectiveness Rates] Optimal Alternative Highlighted**	**Resources; *Key Assumptions***
	CBA	Smoking employees	**biochemically confirmed**; Net monetary benefit; *N/A*	weeks) [16.1%] **3. Brief BC + Varenicline [21.9%]**	smoking employee; *Single intervention at the start of the time horizon*
McAfee 2008	USA; *Oregon Department of Human Services;* **CEA**	Healthcare Payer; 6 months; Adult smokers (consuming >4 cigarettes per day) with a desire to quit	Self-reported 30 day point prevalence cessation rate at 6 months; Cost/additional quitter; *N/A*	1. TC + NRT patch (2 weeks) [10.4%] **2. TC + NRT patch (8 weeks) [15.8%]**	Intervention cost (including overhead costs); *Single intervention at the start of the time horizon*
Salize 2009	Germany; *German Federal Ministry for Education and Research;*	Health Insurer; 1 year; Adult smokers receiving primary care	12 month cessation rate, **biochemically confirmed**; Cost/additional percentage point	1. No intervention [2.7%] 2. GP training and incentives [3.5%] 3. GP training + NRT or Bupropion [12.1%]	Intervention cost (including overhead costs);

Study 1st Author and Year; **Study Quality**	**Country;** **Sponsorship;** **Study Design**	**Study perspective;** **Time Horizon;** **Study population**	**Effectiveness measure;** **Main outcome measure;** ***Relapse Rate***	**Alternatives [Effectiveness Rates]** **Optimal Alternative Highlighted**	**Resources;** ***Key Assumptions***
	CEA		abstinent participants; *N/A*	4. GP training and incentives + NRT or Bupropion [14.6%]	*Single intervention at the start of the time horizon*

Key

BC = Behavioural counselling

TC= Telephone Counselling

GC= Group Counselling

MS= Motivational Support

BA= Brief Advice

SHM= Self Help Material

CDTQ= Cut Down to Quit

SRDMC= Smoking-related disease medical costs

OTC = Over the Counter

OR= Odds Ratio versus placebo

OR*= Odds Ratio versus no intervention

OR**= Odds Ratio versus BC

Usual courses: NRT 12 weeks (If Nasal Spray, longer), Bupropion 7-10 weeks, Varenicline 12 weeks

* Nonsensical cessation rates reported

** Increase in quit rate in relation to comparator

**** Percentage of the study population ceasing smoking because of the intervention

Table 34: Quality Appraisal of Modelling Studies, Chapter 3

Study 1st Author and Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15
Akehurst 1994	Y	Y	Y	Y	N	N	N/A	Y	N	N	N	N	N	Y	Y
Akehurst 1994a	Y	Y	Y	Y	Y	Y	N/A	Y	Y	N	Y	N	N	Y	Y
Annemans 2009	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	N	Y
Bae 2009	Y	N	Y	Y	N	N	Y	Y	Y	Y	Y	N	N	Y	Y
Bauld 2011	Y	Y	Y	Y	Y	N	Y	N	Y	N	Y	N	Y	Y	Y

Study 1st Author and Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15
Bertram 2007	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	N	N	N	Y
Bolin 2006	Y	N	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	N	Y
Bolin 2008	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y
Bolin 2009	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y
Bolin 2009a	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	N	Y
Cornuz 2003	Y	Y	Y	Y	N	N	N/A	N	Y	N	Y	N	N	N	Y
Cornuz 2006	Y	Y	Y	Y	N	N	N/A	N	Y	N	Y	N	N	N	Y
Cromwell 1997	Y	Y	Y	N	N	N	Y	Y	Y	N	Y	N	N	N	Y
Feenstra 2005	Y	Y	N/A	Y	Y	N	Y	N	Y	N	Y	N	N	Y	Y
Fiscella 1996	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N	Y	N	Y
Flack 2007	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	Y	Y
Gilbert 2004	Y	Y	Y	Y	N	N	N/A	N	Y	N	Y	N	Y	N	Y
Godfrey 2005	Y	Y	Y	Y	N	N	N/A	Y	Y	N	Y	N	N	N	Y
Halpern 2000	Y	Y	Y	Y	Y	N	N/A	Y	N	N	N	N	N	Y	Y
Halpern 2007	Y	N	Y	Y	Y	N	N/A	Y	N	N	Y	N	N	N	Y
Heitjan 2008	Y	Y	N/A	Y	Y	N	N/A	Y	Y	N	Y	N	N	Y	Y
Hind 2009	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Hoogendoorn 2008	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	N	Y
Howard 2008	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y
Igarashi 2009	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y
Javitz 2004	Y	Y	Y	N	N	N	N/A	N	Y	N	Y	N	N	Y	Y
Javitz 2004a	Y	Y	N	N	N	N	N	N	Y	N	Y	N	N	N	Y
Kaper 2006	Y	Y	Y	N	N	N	Y	Y	Y	Y	N	N	N	N	Y

Study 1st Author and Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15
Knight 2010	Y	N	N/A	Y	Y	N	Y	Y	Y	Y	N	N	N	Y	Y
Levy 2002	Y	N	Y	Y	Y	N	N/A	N	Y	N	N	Y	N	N	Y
Levy 2006	Y	N	Y	Y	Y	N	N/A	Y	Y	N	Y	N	Y	N	Y
Linden 2010	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y
McGhan 1996	Y	Y	Y	Y	Y	N	N/A	N	Y	N	N	N	N	Y	Y
Nielsen 2000	Y	Y	Y	Y	Y	N	N/A	Y	Y	N	N	N	N	N	Y
Ong 2005	Y	Y	Y	N	N	N	Y	Y	Y	Y	N	N	Y	Y	Y
Orme 2001	Y	N	Y	Y	Y	N	N/A	Y	Y	N	Y	N	N	Y	Y
Oster 1986	Y	Y	Y	N	N	Y	N/A	Y	Y	N	Y	N	N	N	Y
Plans-Rubio 1998	Y	Y	N	N	N	N	N/A	N	Y	N	Y	N	N	N	Y
Parrott 1998	Y	Y	Y	Y	Y	Y	N/A	Y	N	N	Y	N	N	Y	Y
Shanahan 2003	Y	Y	Y	N	N	N	N/A	N	N	N	N	N	N	Y	Y
Shearer 2006	Y	Y	Y	N	N	Y	N/A	Y	Y	N	N	N	N	N	Y
Song 2002	Y	Y	Y	N	Y	Y	Y	N	Y	N	N	N	N	N	Y
Stapleton 1999	Y	Y	Y	N	N	N	N/A	Y	Y	N	Y	N	N	N	Y
Thavorn 2008	Y	Y	Y	Y	Y	N	N/A	Y	Y	Y	Y	N	N	N	Y
Tran 2010	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Vemer 2010	Y	N	Y	Y	Y	N	Y	Y	Y	N	Y	N	N	N	Y
Wang 2008	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	N	Y	N	Y
Warner 2004	Y	N	Y	Y	Y	N	N/A	Y	Y	N	Y	N	N	N	Y
Wasley 1997	Y	Y	Y	N	N	N	N/A	Y	Y	N	Y	N	Y	N	Y
Welton 2008	Y	N	N/A	N	N	N	Y	Y	Y	Y	N	Y	N	N	Y
Woolacott 2002	Y	Y	Y	N	Y	Y	Y	N	Y	N	N	N	N	Y	Y

Description of questions [15, 136]:

Q1: Was a well-defined question posed in answerable form, in response to a clearly stated decision problem?

Q2: Were the alternatives clearly and fully described (i.e. was treatment length reported?)?

Q3: Were model inputs consistent with the study perspective and scope of the model?

Q4: Was the model type stated?

Q5: Was the model structure clearly described and were structural assumptions clear? (If a model schematic was not reported was the model structure otherwise described? Were health states in state-transition models reported?)

Q6: Were data identification and selection methods appropriate (i.e. systematic)?

Q7: Were the sources for utility weights referenced and appropriate?

Q8: Was an incremental analysis of costs and consequences of alternatives performed?

Q9: Was parameter uncertainty addressed?

Q10: Were the methods used to assess parameter uncertainty appropriate (i.e. probabilistic)?

Q11: Were methodological uncertainties assessed in the sensitivity analysis?

Q12: Were structural uncertainties assessed in the sensitivity analysis?

Q13: Was heterogeneity addressed using sub-group analysis?

Q14: Did the presentation and discussion of study results include all issues of concern to users (i.e. were total costs and outcomes reported?)

Q15: Were conclusions valid, given the data presented?

Table 35: Reasons for Final Stage Exclusions, Chapter 3

Study First Author and Year	**Exclusion Reason**
Abdullah (2004)[469]	Study Design
Abdullah (2008)[470]	Population
Akers (2007)[471]	Alternatives
Apelberg (2010)[472]	Study Design
Barnett (2008)[473]	Population
Bolin (2007)[474]	Study Design
Brandon (2004)[475]	Alternatives
Buck (2000)[121]	Alternatives
Burns (2007)[476]	Study Design
Carpenter (1998)[477]	Population
Cheung (1997)[478]	Study Design
Chirikos (200)[479]	Alternatives

Study First Author and Year	**Exclusion Reason**
Cohen (1998)[480]	Other
Coleman (2010)[481]	Alternatives
CRD Report (1998)[482]	Study Design
Crealey (1998)[122]	Alternatives
Croghan (1997)[123]	Alternatives
Croghan (1998)[483]	Study Type
Cummings (2006)[484]	Study Design
Cummings (1989)[125]	Alternatives
Curry (1998)[126]	Alternatives
Davis (1994)[485]	Study Design
Dey (1999)[486]	Study Design
DiFranza (2001)[487]	Alternatives
Ershoff (1990)[488]	Population
Fellows (2007)[489]	Alternatives
Fosnocht (1998)[490]	Study Design
Godfrey (2002)[491]	Study Design
Gomel (1998)[492]	Alternatives
Hawk (2006)[493]	Study Design
Hill (2006)[189]	Other
Hoogendoorn (2010) [494]	Study Design
Hudmon (1997)[495]	Population
Hueston (1994)[496]	Population
Jiminez (2003)[497]	Other
Johansson (2005)[498]	Alternatives

Study First Author and Year	**Exclusion Reason**
Jones (1998)[499]	Alternatives
Kahende (2009)[500]	Study Design
Keating (2010)[501]	Study Design
Keating (2010b)[502]	Study Design
Keiding (2009)[503]	Study Design
Krumholz (1993)[129]	Alternatives
Lickteig (1993)[504]	Study Design
Meenan (1998)[505]	Alternatives
Miller (1996)[506]	Population
Pinget (2007)[507]	Alternatives
Plans (1995)[508]	Other
Pollack (2001)[509]	Population
QIS (2001)[510]	Study Design
Ranson (2002)[511]	Alternatives
Raw (2005)[512]	Study Design
Raw (1998)[513]	Study Design
Ronckers (2003) [514]	Alternatives
Ronckers (2005) [515]	Study Design
Ruger (2008)[516]	Population
Ruger (2008b)[517]	Alternatives
Saeterdal (2010)[518]	Other
SCTAHC (2002) [519]	Other
Secker-Walker (2005) [520]	Alternatives
Slatore (2009)[521]	Alternatives

Study First Author and Year	**Exclusion Reason**
Solberg (2006)[522]	Alternatives
Stevermer (1996)[523]	Study Design
Tillgren (1993)[524]	Alternatives
Tomson (2004)[525]	Alternatives
Tran (2002)[526]	Population
Tsevat (1992)[527]	Study Design
Warner (1997)[528]	Study Design

11.3. Appendix C: Appendix to Chapter 4

Figure 23: Search Strategy, Chapter 4

Medline: Performed 28th February 2011; limited to studies published after 31st December 2008

1. Economics/

2. exp "Costs and Cost analysis"/

3. "Value of Life"/

4. Economics, Dental/

5. exp Economics, Hospital/

6. Economics, Medical/

7. Economics, Nursing/

8. Economics, Pharmaceutical/

9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.

11. (expenditure$ not energy).ti,ab.

12. (value adj1 money).ti,ab.

13. budget$.ti,ab.

14. 10 or 11 or 12 or 13

15. 9 or 14

16. letter.pt.

17. editorial.pt.

18. historical article.pt.

19. 16 or 17 or 18

20. 15 not 19

21. Animals/

22. Humans/

23. 21 not (21 and 22)

24. 20 not 23

25. (metabolic adj cost).ti,ab.

26. ((energy or oxygen) adj cost).ti,ab.

27. 24 not (25 and 26)

28. *Alcohol Drinking/

29. exp Alcohol-Related Disorders/

30. *Temperance/

31. Alcohol Deterrents/

32. exp Self-Help Groups/

33. "alcohol drinking".mp.

34. Alcoholism.mp.

35. dipsomania.mp.

36. "alcohol consumption".mp.

37. (drink$ adj Excess$).tw.

38. (drink$ adj binge).tw.

39. (drink$ adj heavy).tw.

40. (drink$ adj hazard$).tw.

41. (drink$ adj problem$).tw.

42. (drink$ adj abuse).tw.

43. (drink$ adj dependen$).tw.

44. (drink$ adj harm$).tw.

45. (alcohol$ adj excess$).tw.

46. (alcohol$ adj binge).tw.

47. (alcohol$ adj heavy).tw.

48. (alcohol$ adj hazard$).tw.

49. (alcohol$ adj problem$).tw.

50. (alcohol$ adj abuse).tw.

51. (alcohol$ adj misus$).tw.

52. (drink$ adj misus$).tw.

53. (alcohol$ adj dependen$).tw.

54. (alcohol$ adj harm$).tw.

55. "alcohol intake".tw.

56. or/28-55

57. 27 and 56

58. Rehabilitation Centers/

59. Health Behavior/

60. Health Education/

61. Preventive Health Services/

62. Preventive Psychiatry/

63. Directive Counseling/

64. exp Behavior Therapy/

65. exp Cognitive Therapy/

66. exp Evidence-Based medicine/

67. Hospitalization/

68. (Referral and Consultation).mp.

69. Health Promotion/

70. Health Maintenance Organizations/

71. "relapse prevention".mp.

72. "harm reduction".mp.

73. (naltrexone or acamprosate or disulfiram or opioid-antagonist or antabuse or vivitrol).tw.

74. campral.mp.

75. anti?craving.tw.

76. dis?lfiram.tw.

77. disulfiram.tw.

78. dissulfiram.tw.

79. disulfuram.mp.

80. "brief intervention".tw.

81. "motivational interviewing".tw.

82. "motivational enhancement therapy".tw.

83. "social behavio?r".tw.

84. "cognitive behavio?ral therapy".tw.

85. "aversion therapy".tw.

86. "relapse prevention".tw.

87. "skills training".tw.

88. treatment.mp.

89. or/58-88

90. 57 and 89

NHS EED (via CRD), performed February 2011, limited to studies published after 31st December 2008; HTA (via CRD), performed February 2011, no time restriction imposed

1. MeSH Alcohol-Related Disorders EXPLODE 1 2
2. MeSH Alcohol Drinking EXPLODE 1
3. MeSH Temperance EXPLODE 1
4. MeSH Alcohol Deterrents EXPLODE 1
5. "alcohol drinking"
6. alcoholism
7. dispomania
8. "alcohol consumption"

9. drink* NEAR excess*
10. drink* NEAR binge
11. drink* NEAR heavy
12. drink* NEAR hazard*
13. drink* NEAR problem*
14. drink* NEAR abuse
15. drink* NEAR misus*
16. drink* NEAR dependen*
17. drink* NEAR harm*
18. alcohol* NEAR excess*
19. alcohol* NEAR binge
20. alcohol* NEAR heavy
21. alcohol* NEAR hazard*
22. alcohol* NEAR problem*
23. alcohol* NEAR abuse
24. alcohol* NEAR misus*
25. alcohol* NEAR dependen*
26. alcohol* NEAR harm*
27. "alcohol intake"
28. #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 or #25 or #26 or #27

29. acamprosate OR antabuse OR disulfiram OR vivitrol OR naltrexone

30. #29 OR #30

Table 36: Extracted Data from Economic Evaluation Studies in the Review, Chapter 4

Study 1st Author and Year:	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
Modelling Studies					
Barbosa 2010a	UK; *Various author-specific research funding;* **CUA;** State-transition cohort	Healthcare Payer; Lifetime; Problem drinkers seeking treatment (hazardous and harmful) aged >=16 years; **3.5% p.a.**	12 month probabilities of transition between consumption-specific health states; Cost/QALY gained; *Epidemiological data for health effects;* *'long-term follow-up trial data to inform long run alcohol use'*	1. ME Therapy (3x50 minutes) 2. SB&N Therapy (8x50 minutes) (taken from Russell *et al*)	Intervention cost, ARDC *Lifetime exposure to alcohol interventions equal across consumption-specific health states*
Cobiac 2009	Australia; *Alcohol*	Healthcare payer, patient;	Reduction of alcohol intake per day	**1. BI + follow up [6.3g]** 2. Residential detoxification	Intervention cost, patient

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
	Education and Rehabilitation Foundation; **CUA;** State-transition cohort	Lifetime; Hazardous and harmful drinkers aged 18-79 years (Alternative 1); Dependent drinkers aged 18-79 years (Alternatives 2 & 3); **3% p.a.**	(grams); Cost/DALY gained; *Epidemiological data for health effects; relapse data for alcohol status post follow-up*	(3 weeks) [13g, 50% relapse/year] 3. Residential detoxification + Naltrexone (12 weeks) [13g, 18% relapse/year]	travel and time costs, ARDC; *Authors target 2% of study population for Alternative 1, 4% for Alternatives 2 and 3, but make no explicit assumptions about patient motivation; Single intervention at the start of the model*
Corry 2004	Australia;	Government;	Unspecific	1. Contact with a health	Intervention

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
	Australian Health and Medical Research Council; *Australian Commonwealth Department of Health and Ageing;* **CUA;** Decision Tree	12 months; Alcohol use disorder (ICD-10) (principal complaint) individuals reporting previous contact with the health system for mental problems such as stress, depression or substance dependence; **N/A**	consumption-related symptom change; Cost/Years Lived with Disability averted; *Disability weights*	professional including BC for harmful users and medication for dependent users 2. Optimal care for harmful and dependent users including inpatient detoxification for those with dependency	cost; *Single intervention at the start of the model*
Doran 2004	Australia; *Not clear;* **CEA;** Decision tree	Healthcare payer; 12 months; Primary care patients	Detection rate, Patient coverage, BI effectiveness in modifying drinking;	1. GP screening + BI for at-risk drinkers 2.Improved at-risk drinker detection rate	Intervention cost, detection cost;

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
		aged >=14 years; **N/A**	Cost/number of individuals who have modified their drinking; *N/A*	3. Improved patient coverage of BI 4. Improved effectiveness of BI 5. Joint increases in detection of at-risk drinkers, coverage and effectiveness of BI	*Single intervention for each individual, occurring throughout the time horizon*
Gentilello 2005	USA; *Robert Wood Johnson Foundation;* **CBA;** State-transition cohort	Healthcare payer; 3 years; Trauma centre patients aged >=18 years with high blood-alcohol or an alcohol disorder as defined by a standard questionnaire; **3% p.a.**	Reduction in injuries requiring hospital admission over 3 years of follow-up; Net Benefit; *N/A*	1. No intervention [N/A] **2. BI [48%]**	Intervention cost, detection cost, cost of emergency visits and hospitalisation; *Single intervention for each individual in year one; Acceptance*

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
					rate for treatment of 76%
Lindholm 1998	Sweden; *Swedish Institute for Public Health;* **CEA;** State-transition cohort	Healthcare payer; 30 years; Males aged 40 years comprising 'heavy' drinkers; **5% p.a.**	Change in consumption from 'heavy' to 'moderate'; Cost/Life Year gained; *Epidemiological data on mortality from 'heavy' and 'moderate' drinking assumption used: double mortality risk for heavy drinkers versus everyone else age 40-70; simple assumptions about duration of consumption effect*	1. No Intervention 2. 5 GP visits involving BI (12 months) 3. 25 GP visits involving BI (5 years)	Intervention cost, detection cost, Future general medical costs; *Interventions in first five years of the model*

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
Mortimer 2005	Australia; *Australian Government Department of Health and Ageing; Monash University;* **CUA;** State-transition cohort	Healthcare payer; Lifetime; Heavy drinkers >= 19 years old and hazardous drinkers not physically dependent 17-70 years old (Alternative 1); Patients seeking help for alcohol problems and drinkers 15-59 years old (Alternative 2); Detoxified patients with history of severe dependence but	Change in proportion of patients drinking at 12 months (typical); Cost/QALY gained; *Movement between drinking level health states adjusted for HRQoL using disability weights;* *'pessimistic' assumptions about duration of effect from limited follow-up data post 1 year*	1. BI for problem drinking; 2. Psychotherapy for mild to moderate dependence; 3. Drug therapy + counselling for detoxified dependent drinkers	Intervention cost, ARDC in sensitivity analysis only; *Single intervention at the start of the model*

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
		no other substance dependence (Alternative 3); **5% p.a.**			
Neighbors 2010	USA; *NIAAA; National Cancer Institute;* **CUA;** Decision Tree	Healthcare payer; Societal; Lifetime; Emergency department hospital patients aged 18-19 years admitted for alcohol-related injuries; **3% p.a.**	Drink driving incidence rate, alcohol-related injury rate, traffic ticket rate; Cost/QALY gained; *National mortality tables to estimate death rates from drink driving and population-level utility data; alcohol level itself not linked directly to health*	1. BA **2. Motivational Interview**	Intervention cost, accident fatality costs; *Single intervention at the start of the model; Acceptance rate for treatment of 67%; no consideration of long term effects, just*

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
					simple extrapolation assumption.
NICE 2010	UK; *NHS NICE;* ***CUA;*** Decision Tree	Healthcare payer; End of Hospital admission; Hospital patients with acute alcohol withdrawal; **3.5% p.a.**	Difference in length of hospital stay compared to Placebo; Cost/QALY gained; N/A; *Utility scores from effectiveness trials*	1. Placebo 2. Oxazepam 3. Chlordiazepoxide 4. Clomethiazole 5. Lorazepam	Intervention cost; *Ongoing treatment for each individual throughout time horizon*
NICE 2011	UK; *NHS NICE;* ***CUA;*** Decision Tree (from Schadlich et al)	Healthcare payer; 12 months; Individuals in recovery from alcohol dependence; **N/A**	Abstinence rate at 12 months; Cost/QALY gained; *Utility scores from published studies*	1. Psychological therapy to prevent relapse [10.44%] **2. Psychological therapy + Acamprosate [17.47%]** 3. Psychological therapy + Naltrexone [18.24%]	Intervention cost, Relapse cost; *Single intervention at the start of the model*

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
Palmer 2000	Germany; *Not clear;* **CEA;** State-transition cohort	Healthcare payer; Lifetime; Male detoxified alcoholic patients, 80% with fatty liver, 15% with cirrhosis, 22% with chronic pancreatitis, 1% with cardiomyopathy; **5% p.a.**	Abstinence rate; Cost/Life Year gained; *Incidence of ARD among abstinent and relapsed patients translated to survival rates;* *abstinence rates reduce according to unreported function after 2 years and remain constant after five years*	1. BC **2. BC + Acamprosate (48 weeks)**	Intervention cost, ARDC; *Single intervention at the start of the model*
Purshouse 2008	UK; *NHS NICE*; **CUA**; State-transition cohort	Healthcare payer; 30 years; General English population; **3.5% p.a.**	Reduction in mean consumption at 12 months; Cost/QALY gained; *Assumptions about*	1. Screening at next GP registration for 10 years 2. Screening at next primary care appointment for 10 years	Intervention cost, ARDC; *Uptake of interventions;*

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
			duration of effect and statistical equations linking consumption to harm	3. Screening in emergency care for 10 years	*long run effectiveness*
Quanbeck 2010	USA; *Various author-specific research funding;* **CBA;** State-transition cohort	Employer; 4 years; Individuals aged 18-65 years in primary care screening positive for problem drinking; **3.5% p.a.**	Alcohol consumption change (7 days), binge drinking episode rate (30 days); Net monetary benefit; *Estimates of absenteeism attributable to alcohol abuse*	1. General health booklet **2. BI + reinforcement telephone call**	Intervention cost, cost of problem drinking to an employer; *Not clear if intervention was available throughout time horizon or solely at the start of the model*
Schadlich 1998	Germany; *Lipha*	Healthcare payer; 96 weeks;	Abstinence rate at 96 weeks;	1. BC + Placebo (48 weeks) [17.3%]	Intervention cost, ARDC;

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
	Arzneimittel GmbH; ***CUA;*** Decision tree	Alcohol dependent (DSM-III) psychiatric outpatients abstinent for 14-28 days; **5% p.a.**	Cost per additional abstinent patient; *N/A*	**2. BC + Acamprosate (48 weeks) [39.9%]**	*Single intervention at the start of the model*
Slatterly 2003	UK; *NHS Scotland;* **CEA;** Decision tree	Healthcare payer and patient; 20 years; Newly abstinent and detoxified alcohol dependent individuals; **6% p.a. for costs only**;	Number of patients with abstained or controlled drinking at close to 12 month; Cost/abstinent or controlled drinker at 20 years; *Relapse rate estimates*	1. Placebo or No Intervention [OR: 1.00] 2. Coping / Social Skills Training [OR: 2.11] 3. BC (Self Control) [OR: 1.75] 4. ME Therapy [OR: 1.88] 5. Marital / Family Therapy [OR: 1.94] 6. Acamprosate (12 months) [OR*: 1.73] 7. Naltrexone (6 months) [OR*: 1.46]	Intervention cost, ARDC; *Single intervention at the start of the model*

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
				8. Disulfiram (6 months) [OR*: 1.31]	
Tariq 2009	Netherlands; *Ministry of Health, Welfare and Sport of the Netherlands;* **CUA;** State-transition cohort	Healthcare payer; Lifetime; Primary care patients aged 20 to 65 years; **4% p.a. for costs, 1.5% p.a. for benefits;**	Decrease in consumption at 12 months; Cost/QALY gained; *Risk ratios for ARDs to estimate survival among different drinking groups, national disability weight data; mysterious 'long term maintenance fraction' for long term reduction in alcohol consumption*	1. No intervention 2. Screening + BI for excessive drinkers	Intervention costs, Future general medical expenditure; *Single intervention in year one of the model*
Wutzke 2001	Australia; *National Health and Medical*	Healthcare payer; Lifetime; Hazardous and	Number of 'at risk' drinkers identified; Decrease in alcohol	1. No training or support (for health practitioners implementing BI)	Cost of marketing to health

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
	Research Council of Australia; **CEA;** State-transition cohort	harmful drinkers aged >=16 years; **3% p.a.**	consumption among 'at risk' drinkers; Cost/Life Year gained; *Implicit assumption of sustained consumption effect*	2. Training (5 minutes) only 3. Training + fortnightly advice 4. Training + fortnightly telephone or personal visits	professionals, Training and support costs, Intervention costs; *Single intervention in first three months of the model*
Primary Studies					
Alwyn 2004	UK; *Not clear;* **CEA;** N/A	Healthcare payer; 12 months; Home detoxification patients; **N/A**	Number of days abstinent, drinks/day total consumption. Other measures included; Costs and outcomes	1. Home detoxification with medication 2. Home detoxification with medication + Psychological Therapy	Intervention cost; *Single intervention at the start of the*

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
			reported separately; *N/A*		*time horizon*
Babor 2006	USA; *Robert Wood Johnson Foundation;* **CEA;** N/A	Healthcare payer; 12 months; At-risk drinkers undergoing home detoxification; **N/A**	Number of drinks/week; Costs and outcomes reported separately; *N/A*	1. BI in 'usual care' 2. BI delivered by licensed practitioners 3. BI delivered by mid-level health professionals	Intervention cost; *Single intervention at the start of the time horizon*
Barrett 2006	UK; *Alcohol Education and Research Council;* **CEA;** N/A	Societal; 12 months; Hazardous drinkers in an accident and emergency department of a general hospital; **N/A**	Units of alcohol consumed/week; Cost/unit reduction in alcohol consumption/week; *N/A*	1. Information Leaflet **2. BI from an Alcohol Health Worker**	Intervention cost, social care costs, criminal justice costs, productivity costs; *Single intervention at the start of the*

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
					time horizon
Bischof 2008	Germany; *German Federal Ministry of Research and Education;* **CEA;** N/A	Healthcare payer; 12 months; At-risk, dependent, alcohol abusing and heavy episodic drinkers aged 18-64 years in primary care; **N/A**	Alcohol consumption/day, number of binge episodes; Costs and outcomes reported separately; *N/A*	1. No Intervention 2. Computerized intervention + BC (up to 3x30 mins) 3. Computerized intervention + BC (fixed 4x30 mins)	Intervention cost (counsellor cost only); *Single intervention at the start of the time horizon*
Drummond 2009	UK; *Wales Office for Research and Development;* **CUA;** N/A	Societal; 6 months; Male hazardous drinkers who had not received treatment for an alcohol use disorder in at least 180 days;	Total alcohol consumed (over 180 days), mean number of drinks per drinking day, percentage of days abstinent; Cost/QALY gained; *EQ-5D published*	1. Minimal Nurse Intervention 2. Stepped Care: BC + MET (4x50 mins) + referral to alcohol treatment agency	Intervention cost, Training cost, general healthcare costs, social care costs, criminal justice costs, costs associated

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
		N/A	*estimates*		with accidents; *Single intervention at the start of the time horizon*
Dunlap 2010	USA; *NIAAA;* **CEA;** N/A	Patient; 16 weeks; Individuals with alcohol dependence (DSM-IV) abstinent for 4-21 days; **N/A**	Percent of days abstinent, proportion avoiding heavy drinking, proportion achieving 'good' clinical outcome; Cost/additional percentage point or patient positive for each of the 3 primary outcome measures; *N/A*	1. Placebo + MM 2. BC 3. Naltrexone (16 weeks) + MM 4. Acamprosate (16 weeks) + MM 5. Placebo + MM + BC 6. Naltrexone (16 weeks) + Acamprosate + MM 7. Naltrexone (16 weeks) + MM + BC 8. Acamprosate (16 weeks) + MM + BC 9. Naltrexone (16 weeks) +	Patient time, medication and travel costs; *Single intervention at the start of the time horizon*

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
				Acamprosate (16 weeks) + MM + BC	
Fals-Stweart 2005	USA; *National Institute on Drug Abuse; NIAAA; Alpha Foundation;* ***CEA;*** N/A	Healthcare payer and patient; 12 months; Alcohol dependent (DSM-IV) male aged 20-60 years who has a partner; **N/A;**	Percentage of Days of Heavy Drinking; Change in Percentage of Days of Heavy Drinking/Cost weight; *N/A*	1. Brief Relationship Therapy 2. Shortened standard Behavioural Couples Therapy 3. Individual-based Treatment 4. Psycho-educational Attention Control Treatment	Intervention cost, Patient time and travel costs; *Single intervention at the start of the time horizon*
Fleming 2002	USA; *Robert Wood Johnson Foundation; NIAAA; National Institutes of Health;* **CEA; CBA;** N/A	Healthcare payer and patient; Societal; 2 years; Individuals aged 18-65 years in primary care screening positive for problem	Alcohol consumption change (7 days), binge drinking episode rate (30 days); Net monetary benefit; *Utilisation of health care, motor vehicle*	1. General health booklet **2. BI + reinforcement telephone call**	Intervention cost, Patient time cost (Healthcare payer and patient perspective only), Health service

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
		drinking; **0% p.a.**	*events and legal events*		utilisation cost (Societal perspective only), Legal and motor vehicle accident costs (Societal perspective only); *Single intervention at the start of the time horizon*
Humphreys 1996	USA; *NIAAA; Department of Veterans Affairs;*	Healthcare payer; 3 years; Individuals seeking help for	Number of days intoxicated in past month, ounces of ethanol consumed	1. Professional outpatient alcoholism treatment 2. AA self-help and mutual aid programme	Treatment costs (excluding costs for major

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
	CEA; N/A	alcoholism with no previous treatment; **5% p.a. for costs**	on a typical drinking day. Other measures included; Costs and outcomes reported separately; *N/A*		surgical procedures related to alcoholism) for Alternative 1 only; *Single intervention at the start of the time horizon*
Kunz 2004	USA; *NIAAA; National Institutes for Health;* **CEA;** N/A	Healthcare payer; 3 months; Hospital emergency department patients screening positive for alcohol problems; **N/A**	AUDIT score, average drinks/week, percentage of patients heavy drinking; Cost/each primary outcome measure; *N/A*	1. Information packet 2. Information packet + BI	Intervention cost; *Single intervention at the start of the time horizon*

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
Lock 2006	UK; *NHS;* **CEA;** N/A	Healthcare payer and patient; 12 months; Patients aged >=16 years screened for alcohol use disorders in primary care; **N/A**	Number of drinks/drinking day, Drinking Problems Index, SF-12 HRQoL questionnaire; Costs and outcomes reported separately; *N/A*	1. Information Leaflet + BA 2. BI	Intervention cost, Patient time, travel, accident and property damage costs; *Single intervention at the start of the time horizon*
Long 1998	UK; *Not clear;* ***CEA;*** N/A	Healthcare payer; 12 months; Alcohol dependent (ICD-10) individuals; **N/A**	Proportion of abstinent days, consumption. Other measures included; Costs and outcomes reported separately; *N/A*	1. Residential programme (5 weeks) **2. In- and day-patient programme (2 weeks)**	Intervention cost; *Single intervention at the start of the time horizon*
Moraes 2010	Brazil; *State of Sao*	Societal (healthcare payer	Abstinence rate. Other measures	1. Outpatient detoxification involving 20 group sessions	Intervention cost, Patient

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
	Paolo Research Foundation; **CEA; CUA;** N/A	+ patient costs); 3 months; Alcoholic patients aged 20-66 years **N/A**	included such as SF-36; Incremental Cost/Incremental Abstinence; *N/A*	(3 months) [43.1% (3.4% at baseline)] **2. Outpatient detoxification involving 20 group sessions (3 months) + 4 Home Visits to enhance patient and family adherence [58.11% (1.6% at baseline)]**	travel and time (productivity) costs; *Single intervention at the start of the time horizon*
Nalpas 2003	France; *French Ministry of Health; Fonds d'Intervention en Santé Publique; the LIPHA group;* **CEA;** N/A	Healthcare payer and employer; 12 months; Alcohol dependent (DSM-IV) patients aged >=18 years admitted to specialist centres for detoxification; **N/A**	Number of months without relapse; Costs and outcomes reported separately; *N/A*	1. Detoxification + follow up (Centre 1) 2. Detoxification + follow up (Centre 2) 3. Detoxification + follow up (Centre 3) 4. Detoxification + follow up (Centre 4)	Intervention cost, Productivity costs; *Single intervention at the start of the time horizon*

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
O'Farrell 1996	USA; *NIAAA; Department of Veterans Affairs; the Smithers Foundation;* **CEA;** N/A	Societal; 3 years (1 year pre-intervention, 2 years post-intervention); Newly abstinent married males (with non-alcoholic spouses) under outpatient counselling for alcoholism; **0% p.a.**	Percent of days abstinent, marital satisfaction; Units of improvement for each outcome measure/Weighted Cost; *N/A*	**1. Individual BC** 2. Individual BC + Behavioural Marital Therapy (involving Antabuse Contract) 3. Individual BC + Interactional Couples Therapy (not involving Antabuse Contract)	Intervention cost, ARDC, criminal justice costs; *Single intervention at the start of the time horizon*
Parrott 2006	UK; *Department of Health;* **CEA; CUA;** N/A	Societal; 6 months; Individuals with alcohol dependence; **N/A**	Reduction in ethanol consumption at 60 days; Cost/QALY gained; *EQ-5D questionnaire scores*	1. Partially-hospitalised NHS daytime detoxification service (3 days) 2. Inpatient charity-funded detoxification service (10 days)	Intervention cost, social service costs, criminal justice system costs; *Single*

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
					intervention at the start of the time horizon
Pettinati 1999	USA; *NIAAA;* **CEA;** N/A	Healthcare payer; 12 months; Alcohol dependent (DSM-III) patients with no other substance dependencies; **N/A**	'Significant drinking' of 3 or more drinks per day rates; Cost/probability of returning to 'Significant drinking'; N/A	1. Inpatient AA treatment (4 weeks) 2. Outpatient AA treatment (6 weeks)	Intervention cost; *Single intervention at the start of the time horizon*
Russell 2005	UK; *Medical Research Council; NHS Executive in England; Wales Office for Research & Development in*	Healthcare payer and public sector; 12 months; Individuals seeking treatment for alcohol problems aged >=16;	EQ-5D health outcomes; Cost/additional QALY; *N/A*	1. ME Therapy (3x50 minutes) 2. SB&N Therapy (8x50 minutes)	Healthcare and alcohol treatment costs, social service costs, criminal justice system costs;

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
	Health and Social Care; **CUA;** N/A	**N/A**			*Single intervention at the start of the time horizon*
Rychlik 2003	Germany; *Merck KGaA;* **CEA;** N/A	Healthcare payer and patient; 12 months; detoxified alcohol dependent (DSM-IV) patients aged 18-65 years; **N/A**	Abstinence rate at 12 months; Cost/Abstinence rate; *N/A*	1. Psychosocial Rehabilitation Program 2. Psychosocial Rehabilitation Program + Acamprosate	Intervention cost, Cost of lost salary from time spent out of work, Travel costs; *Single intervention at the start of the time horizon*
Shakeshaft 2002	Australia; *National Health and Medical Research*	Service provider; 6 months; Individuals attending a free	AUDIT questionnaire outcomes, weekly and binge consumption. Other	**1. Pamphlet + BI** 2. Cognitive BT	Intervention cost; *Single*

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
	Council; ***CEA;*** N/A	community-based substance abuse counselling service; **N/A**	measurements included; Cost/Mean effectiveness across outcome measures index; *N/A*		*intervention at the start of the time horizon*
Sobell 2002	Canada; *NIAAA;* ***CEA;*** N/A	Healthcare payer; 12 months; Alcohol abusers (more than 12 drinks per week or over 4 drinks on over 4 days in the past week) who had never sought help or treatment; **N/A**	Alcohol consumption/week, number of days drinking and binge drinking. Other measures included. Costs and outcomes reported separately; *N/A*	**1. Pamphlets** 2. BA + feedback	Recruitment costs, Intervention cost; *Single intervention at the start of the time horizon*
Walters 2009	Australia;	Healthcare payer;	Abstinence rate	1. BC (12 weeks)	Intervention

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
	Internal Funds; **CUA;** N/A	12 weeks; Alcohol dependent (DSM-IV) adults with no other substance dependencies; **N/A**	(medically confirmed); Cost/successful treatment [No statistical difference in SF-6D scores between groups]; *N/A*	**2. BC + Naltrexone (12 weeks)**	costs; *Single intervention at the start of the time horizon*
Zarkin 2008	USA; *NIAAA;* ***CEA;*** N/A	Healthcare payer; 16 weeks; Individuals with alcohol dependence (DSM-IV) abstinent for 4-21 days; **N/A**	Percent of days abstinent proportion avoiding heavy drinking, proportion achieving 'good' clinical outcome; Cost/additional percentage point or patient positive for each of the 3 primary outcome measures; *N/A*	1. Placebo + MM 2. BC 3. Naltrexone (16 weeks) + MM 4. Acamprosate (16 weeks) + MM 5. Placebo + MM + BC 6. Naltrexone (16 weeks) + Acamprosate + MM 7. Naltrexone (16 weeks) + MM + BC 8. Acamprosate (16 weeks) +	Intervention cost; *Single intervention at the start of the time horizon*

Study 1st Author and Year;	**Country;** **Sponsorship;** **Study design;** **Model Type**	**Study perspective;** **Time horizon;** **Study population;** **Discount rate**	**Effectiveness measure;** **Main outcome measure;** **Long Term Extrapolation**	**Alternatives [Effectiveness Rates]** **Economically optimal alternative highlighted**	**Resources;** ***Key Assumptions***
				MM + BC 9. Naltrexone (16 weeks) + Acamprosate (16 weeks) + MM + BC	

Key

ARDC = Alcohol-Related Disease Costs

ME = Motivational Enhancement

SB&N = Social Behaviour & Network

NIAAA = National Institute on Alcohol Abuse and Alcoholism

BA = Brief Advice

BC = Behavioural Counselling

MM = Medical Management

AA = Alcoholics Anonymous

OR= Odds Ratio versus placebo

OR*= Odds Ratio versus no intervention

DALY = Disability-Adjusted Life Year

p.a. = per annum

Table 37: Quality Appraisal, Chapter 4

Study 1st Author and Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15
Barbosa 2010	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y
Cobiac 2009	Y	Y	Y	Y	N	N	N	N	Y	Y	N	N	N	Y	Y
Corry 2004	Y	Y	Y	Y	N	N	Y	N	Y	Y	N	N	N	Y	Y
Doran 2004	Y	Y	N/A	Y	Y	N	N/A	N	Y	N	N	N	N	Y	Y
Gentilello 2005	Y	Y	Y	Y	Y	NC	N/A	Y	Y	Y	N	N	N	Y	Y
Lindholm 1998	Y	Y	Y	Y	N	N	N/A	N	Y	N	N	N	N	Y	Y
Mortimer 2005	Y	Y	NC	Y	Y	N	Y	Y	Y	N	Y	N	N	Y	Y
Neighbors 2010	Y	Y	Y	N	N	N	N/A	Y	Y	Y	N	N	N	Y	Y
NICE 2010	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N	N	N	Y	Y
NICE 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y
Palmer 2000	Y	Y	Y	Y	Y	N	N/A	Y	Y	N	N	N	N	Y	Y
Purshouse 2008	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	N	Y	Y	Y
Quanbeck 2010	Y	Y	Y	Y	N	N	N/A	Y	Y	N	N	N	N	Y	Y
Schadlich 1998	Y	Y	Y	Y	Y	N	N/A	Y	Y	N	N	N	N	Y	Y
Slatterly 2003	Y	Y	Y	Y	Y	Y	N/A	N	Y	N	Y	N	N	Y	Y
Tariq 2009	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	N	Y	Y
Wutzke 2001	Y	Y	Y	Y	N	N	N/A	N	Y	N	Y	N	N	Y	Y

Table 38: Reasons for Final Stage Exclusions, Chapter 4

Study First Author and Year	**Exclusion Reason**
Berglund (2001)[529]	Other
Gifford (2010) [530]	Population
Harwood (2009)[531]	Population
HAYES (2009a)[532]	Other
HAYES (2009b)[533]	Other
HAYES (2010)[534]	Other
Kapoor (2009)[535]	Alternatives
Mitchell (2009a)[536]	Other
Mitchell (2009b)[537]	Other
Mitchell (2009c)[538]	Other
Olmstead (2010)[539]	Population

11.4. Appendix D: Appendix to Chapter 5

Table 39: Attrition bias test results, At-risk drinking participation equation, full unbalanced sample

Tests for attrition bias				
Equations modelling the probability of participation in 'at risk' drinking				
Men	Static Probit	Number of waves participant present	Chi2(1)	2.65
			Probability > Chi2	0.1038
		Participant present in all waves	Chi2(1)	1.67
			Probability > Chi2	0.1963
		Participant present in next wave	Chi2(1)	0.25
			Probability > Chi2	0.6194
	Dynamic probit model with random effects	Number of waves participant present	Chi2(1)	0.52
			Probability > Chi2	0.4717
		Participant present in all waves	Chi2(1)	0.13
			Probability > Chi2	0.7235
		Participant present in next wave	Chi2(1)	0.32
			Probability >	0.5727

Tests for attrition bias

Equations modelling the probability of participation in 'at risk' drinking

			Chi2	
Women	Static Probit	Number of waves participant present	Chi2(1)	0.70
			Probability > Chi2	0.4013
		Participant present in all waves	Chi2(1)	1.50
			Probability > Chi2	0.2208
		Participant present in next wave	Chi2(1)	2.72
			Probability > Chi2	0.0992
	Dynamic probit model with random effects	Number of waves participant present	Chi2(1)	1.37
			Probability > Chi2	0.2415
		Participant present in all waves	Chi2(1)	1.88
			Probability > Chi2	0.1705
		Participant present in next wave	Chi2(1)	2.15
			Probability > Chi2	0.1423

Table 40: Attrition bias test results, Smoking participation equation, full unbalanced sample

Wald test for attrition bias				
Equations modelling the probability of smoking participation				
Men	Static Probit	Number of waves participant present	Chi2(1)	5.39
			Probability > Chi2	0.0202
		Participant present in all waves	Chi2(1)	3.13
			Probability > Chi2	0.0768
		Participant present in next wave	Chi2(1)	0.90
			Probability > Chi2	0.3431
	Dynamic probit model with random effects	Number of waves participant present	Chi2(1)	13.59
			Probability > Chi2	0.0002
		Participant present in all waves	Chi2(1)	9.51
			Probability > Chi2	0.0020
		Participant present in next wave	Chi2(1)	1.29
			Probability > Chi2	0.2561
Women	Static Probit	Number of waves participant present	Chi2(1)	7.23

Wald test for attrition bias			
Equations modelling the probability of smoking participation			
		Probability > Chi2	0.0072
	Participant present in all waves	Chi2(1)	3.14
		Probability > Chi2	0.0762
	Participant present in next wave	Chi2(1)	1.30
		Probability > Chi2	0.2548
Dynamic probit model with random effects	Number of waves participant present	Chi2(1)	16.95
		Probability > Chi2	0.0000
	Participant present in all waves	Chi2(1)	8.67
		Probability > Chi2	0.0032
	Participant present in next wave	Chi2(1)	0.74
		Probability > Chi2	0.3883

Table 41: Comparison of model estimates before and after re-weighting for attrition

Probability of smoking participation Univariate static probit model	Men				Women			
	Un-weighted		Weighted		Un-weighted		Weighted	
	Raw coefficients	Average partial effects	Raw coefficients	Average partial effects	Raw coefficients	Average partial effects	Raw coefficients	Average partial effects
Explanatory variables								
Smoker last year	2.098***	0.585***	2.095***	0.593***	2.209***	0.572***	2.221***	0.582***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
At-risk drinker last year	0.090**	0.016**	0.099**	0.019**	0.049	0.006	0.069	0.009
	(0.027)	(0.027)	(0.018)	(0.018)	(0.370)	(0.370)	(0.221)	(0.221)
Initial value smoker	1.110***	0.263***	1.088***	0.267***	1.074***	0.203***	1.040***	0.198***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
Initial value at-risk drinker	-0.008	-0.001	0.002	0.000	0.057	0.007	0.048	0.006
	(0.852)	(0.852)	(0.958)	(0.958)	(0.356)	(0.356)	(0.444)	(0.444)
Age	-0.005	-0.001	-0.006	-0.001	-0.011	-0.001	-0.012*	-0.001*
	(0.410)	(0.410)	(0.290)	(0.290)	(0.102)	(0.102)	(0.074)	(0.074)
Age squared	-0.000	-0.000	-0.000	-0.000	0.000	0.000	0.000	0.000
	(0.230)	(0.230)	(0.371)	(0.371)	(0.887)	(0.887)	(0.785)	(0.785)
Highest qualification - vocational	-0.010	-0.002	0.023	0.004	0.127	0.016	0.171	0.022
	(0.932)	(0.932)	(0.852)	(0.852)	(0.294)	(0.294)	(0.158)	(0.158)
Highest qualification - graduate	-0.074	-0.013	-0.040	-0.007	-0.046	-0.005	-0.019	-0.002

Probability of smoking participation Univariate static probit model	Men				Women			
	Un-weighted		Weighted		Un-weighted		Weighted	
	Raw coefficients	Average partial effects	Raw coefficients	Average partial effects	Raw coefficients	Average partial effects	Raw coefficients	Average partial effects
	(0.606)	(0.606)	(0.789)	(0.789)	(0.722)	(0.722)	(0.881)	(0.881)
Marital status - separated	0.210*	0.041*	0.183	0.037	0.238**	0.033**	0.246**	0.035**
	(0.074)	(0.074)	(0.111)	(0.111)	(0.038)	(0.038)	(0.040)	(0.040)
Marital status - divorced	0.159	0.030	0.139	0.028	-0.006	-0.001	-0.039	-0.005
	(0.179)	(0.179)	(0.227)	(0.227)	(0.954)	(0.954)	(0.709)	(0.709)
Marital status - widowed	0.236	0.047	0.228	0.048	0.226	0.031	0.221	0.031
	(0.243)	(0.243)	(0.254)	(0.254)	(0.124)	(0.124)	(0.137)	(0.137)
Marital status – never married and not cohabiting	0.266**	0.052**	0.260**	0.053**	0.037	0.004	0.118	0.015
	(0.016)	(0.016)	(0.021)	(0.021)	(0.773)	(0.773)	(0.427)	(0.427)
Marital status – never married but cohabiting	0.201**	0.039**	0.197*	0.040*	0.076	0.009	0.112	0.015
	(0.047)	(0.047)	(0.059)	(0.059)	(0.538)	(0.538)	(0.446)	(0.446)
Child resident	-0.065	-0.011	-0.051	-0.009	-0.004	-0.000	-0.027	-0.003
	(0.242)	(0.242)	(0.375)	(0.375)	(0.956)	(0.956)	(0.708)	(0.708)
Tobacco price index	-0.001	-0.000	-0.001	-0.000	0.001	0.000	0.001	0.000
	(0.609)	(0.609)	(0.595)	(0.595)	(0.718)	(0.718)	(0.628)	(0.628)
Alcohol price index	0.001	0.000	0.001	0.000	-0.008*	-0.001*	-0.008*	-0.001*
	(0.769)	(0.769)	(0.745)	(0.745)	(0.052)	(0.052)	(0.058)	(0.058)
Real household disposable income (natural logarithm)	0.011	0.002	0.006	0.001	0.021	0.002	0.022	0.003
	(0.622)	(0.622)	(0.784)	(0.784)	(0.406)	(0.406)	(0.389)	(0.389)

Probability of smoking participation Univariate static probit model	Men				Women			
	Un-weighted		Weighted		Un-weighted		Weighted	
	Raw coefficients	Average partial effects	Raw coefficients	Average partial effects	Raw coefficients	Average partial effects	Raw coefficients	Average partial effects
Public place smoking ban in operation	-0.085*	-0.015*	-0.085*	-0.016*	0.036	0.004	0.037	0.005
	(0.059)	(0.059)	(0.070)	(0.070)	(0.460)	(0.460)	(0.458)	(0.458)
Own-health subjective measure – good or very good health	0.103**	0.018**	0.115***	0.022***	0.042	0.005	0.058	0.007
	(0.014)	(0.014)	(0.009)	(0.009)	(0.334)	(0.334)	(0.190)	(0.190)
Own-health subjective measure – fair health	0.045	0.008	0.057	0.011	-0.078	-0.009	-0.046	-0.005
	(0.462)	(0.462)	(0.377)	(0.377)	(0.242)	(0.242)	(0.509)	(0.509)
Own-health subjective measure – poor health	-0.104	-0.017	-0.114	-0.020	-0.175	-0.018	-0.102	-0.012
	(0.319)	(0.319)	(0.292)	(0.292)	(0.161)	(0.161)	(0.416)	(0.416)
Constant	-1.805**		-1.709**		-1.201*		-0.934	
	(0.011)		(0.019)		(0.090)		(0.235)	
Observations	31,210	31,210	30,564	30,564	32,904	32,904	32,083	32,083

Note: P-values in parenthesis; parameter estimates for time-averaged explanatory variables not reported

Table 42: Results from Dynamic Univariate Random Effects Probit Models

Variables	Men		Pooled	
	(1) Smoker	(2) At-risk Alcohol Use	(3) Smoker	(4) At-risk Alcohol Use
Smoker last year	1.519***	0.210***	1.628***	0.231***
	(0.000)	(0.002)	(0.000)	(0.000)
At-risk Drinker last year	0.087	0.848***	0.104**	0.830***
	(0.159)	(0.000)	(0.029)	(0.000)
Smoker initial value	2.568***	0.154*	2.441***	0.187***
	(0.000)	(0.055)	(0.000)	(0.002)
At-risk Drinker initial value	0.029	2.425***	0.040	2.440***
	(0.696)	(0.000)	(0.487)	(0.000)
Age	-1.723***	-0.421*	-1.609***	-0.733***
	(0.000)	(0.091)	(0.000)	(0.000)
Male			0.184***	0.318***
			(0.000)	(0.000)
Graduate Education	0.106	0.086	-0.114	-0.107
	(0.593)	(0.626)	(0.501)	(0.463)
Vocational Further Education	0.005	-0.102	0.161	0.078
	(0.983)	(0.657)	(0.232)	(0.532)
Separated	0.327*	-0.141	0.328**	-0.065
	(0.081)	(0.372)	(0.011)	(0.577)
Divorced	0.225	0.040	0.073	-0.096
	(0.255)	(0.808)	(0.595)	(0.424)
Widowed	0.309	-0.159	0.387*	-0.044
	(0.489)	(0.551)	(0.069)	(0.820)
Never married, cohabiting	0.051	0.208	0.041	0.019

Variables	Men		Pooled	
	(1) Smoker	(2) At-risk Alcohol Use	(3) Smoker	(4) At-risk Alcohol Use
	(0.812)	(0.247)	(0.776)	(0.879)
Never married, not cohabiting	0.057	-0.009	0.037	0.267*
	(0.765)	(0.955)	(0.818)	(0.055)
Child(ren) in family home	-0.153	-0.080	-0.128	-0.029
	(0.135)	(0.353)	(0.103)	(0.668)
Tobacco Price Index	-0.464*	-0.205	-0.259	-0.080
	(0.074)	(0.304)	(0.176)	(0.600)
Alcohol Price Index	0.126	0.379	-0.407	0.207
	(0.850)	(0.467)	(0.402)	(0.600)
Natural log of Household Annual Disposable Income	0.011	-0.034	0.033	-0.045**
	(0.739)	(0.239)	(0.178)	(0.042)
Smoking Ban	-0.148**	0.058	-0.109**	0.040
	(0.031)	(0.279)	(0.029)	(0.324)
Good Health	0.148**	0.077	0.140***	0.068*
	(0.020)	(0.133)	(0.002)	(0.075)
Fair Health	0.073	0.072	-0.055	0.083
	(0.446)	(0.365)	(0.429)	(0.166)
Poor Health	-0.061	-0.278*	-0.279**	-0.364***
	(0.728)	(0.072)	(0.027)	(0.002)
Major City	-0.006	0.123	-0.093	0.120
	(0.968)	(0.338)	(0.386)	(0.209)
Intercept	-3.060**	-2.673**	-2.518***	-2.822***
	(0.021)	(0.037)	(0.006)	(0.002)

Variables	Men		Pooled	
	(1) Smoker	**(2) At-risk Alcohol Use**	**(3) Smoker**	**(4) At-risk Alcohol Use**
Natural logarithm of variance of random effect	-0.150	0.305***	-0.259**	0.270***
	(0.332)	(0.001)	(0.028)	(0.000)
Observations; number of respondents	22,162; 4,508	22,162; 4,508	44,646; 9,309	44,646; 9,309
Average number of waves in sample	4.9	4.9	4.8	4.8
Log-likelihood	-3515.80	-5950.82	-6461.84	-10309.759

Note: Parameter estimates for time-averaged explanatory variables not reported

Table 43: Results from Dynamic Univariate Random Effects Probit Model, female sub-sample only

Variables	Women	
	(1) Smoker	(2) At-risk Alcohol Use
Smoker last year	1.765***	0.266***
	(0.000)	(0.001)
At-risk Drinker last year	0.143*	0.794***
	(0.059)	(0.000)
Smoker initial value	2.283***	0.220**
	(0.000)	(0.016)
At-risk Drinker initial value	0.054	2.454***
	(0.553)	(0.000)
Age	-1.410***	-1.289***
	(0.000)	(0.000)
Graduate Education	-0.238	-0.089
	(0.321)	(0.636)
Vocational Further Education	0.215	0.062
	(0.242)	(0.727)
Separated	0.309*	-0.023
	(0.090)	(0.896)
Divorced	-0.059	-0.260
	(0.757)	(0.145)
Widowed	0.384	0.033
	(0.115)	(0.907)
Never married, cohabiting	-0.017	0.071
	(0.939)	(0.727)
Never married, not cohabiting	-0.020	0.358
	(0.935)	(0.107)
Child(ren) in family home	-0.070	0.047
	(0.584)	(0.691)
Tobacco Price Index	0.011	0.090
	(0.970)	(0.702)
Alcohol Price Index	-1.112	0.010
	(0.119)	(0.987)
Natural log of Household Annual Disposable Income	0.060	-0.069*
	(0.112)	(0.059)
Smoking Ban	-0.058	0.019
	(0.427)	(0.760)
Good Health	0.135**	0.062
	(0.045)	(0.290)
Fair Health	-0.212**	0.114
	(0.040)	(0.220)
Poor Health	-0.498***	-0.513***
	(0.006)	(0.009)
Major City	-0.185	0.108
	(0.226)	(0.447)
Intercept	-1.718	-2.863**
	(0.181)	(0.032)
Natural logarithm of variance of random effect	-0.424**	0.203*
	(0.020)	(0.063)

Variables	Women	
	(1) Smoker	(2) At-risk Alcohol Use
Observations; number of respondents	22,484; 4,801	22,484; 4,801
Average number of waves in sample	4.7	4.7
Log-likelihood	-2915.36	-4325.54

Note: Parameter estimates for time-averaged explanatory variables not reported

Table 44: Sample characteristics, 'compact' estimation sample, males only

Variable	Observations	Mean	Standard Deviation	Minimum	Maximum
Smoker	22162	0.22	0.41	0	1
At-risk Drinker	22162	0.22	0.42	0	1
Age	22162	48.76	16.33	17	93
Divorced	22162	0.08	0.27	0	1
Widowed	22162	0.02	0.15	0	1
Separated	22162	0.03	0.18	0	1
Never married, cohabiting	22162	0.07	0.26	0	1
Never married, not cohabiting	22162	0.16	0.37	0	1
Child(ren) residing at family home	22162	0.38	0.48	0	1
Graduate Education	22162	0.40	0.49	0	1
Vocational Further Education	22162	0.24	0.42	0	1
CPI Tobacco	22162	125.19	17.67	107.48	175.47
CPI Alcohol	22162	117.28	8.80	104.32	137.68
Natural logarithm of Household Annual Disposable Income	22162	10.93	0.89	0	13.68
Poor Health	22162	0.03	0.18	0	1
Fair Health	22162	0.15	0.35	0	1
Good Health	22162	0.38	0.48	0	1
Smoking Ban	22162	0.55	0.50	0	1
Major City Residence	22162	0.55	0.50	0	1

Table 45: Sample characteristics, 'compact' estimation sample, pooled sample of men and women

Variable	Observations	Mean	Standard Deviation	Minimum	Maximum
Smoker	44646	0.19	0.39	0	1
At-risk Drinker	44646	0.17	0.37	0	1
Age	44646	0.49	0.16	17	93
Male	44646	0.50	0.50	0	1
Divorced	44646	0.10	0.30	0	1
Widowed	44646	0.06	0.23	0	1
Separated	44646	0.03	0.18	0	1
Never married, cohabiting	44646	0.06	0.25	0	1
Never married, not cohabiting	44646	0.15	0.36	0	1
Married	44646	0.59	0.49	0	1
Child(ren) residing at family home	44646	0.38	0.49	0	1
Graduate Education	44646	0.24	0.42	0	1
Vocational Education	44646	0.33	0.47	0	1
CPI Tobacco	44646	1.25	0.18	107.48	175.47
CPI Alcohol	44646	1.17	0.09	104.32	137.68
Natural logarithm of Household Annual Disposable Income	44646	10.88	0.89	0.00	13.79
Poor Health	44646	0.03	0.18	0	1
Fair Health	44646	0.15	0.36	0	1
Good Health	44646	0.37	0.48	0	1
Smoking Ban	44646	0.55	0.50	0	1
Major City Residence	44646	0.55	0.50	0	1

Table 46:Covariance matrices parameter reference table

Male Sub-sample Estimates	**Pooled Sample Estimates**
Smoking equation	**Smoking equation**
1. L .Smoker	*1. L .Smoker*
2. L. At-risk Drinker	*2. L. At-risk Drinker*
3. Smoker Initial Condition	*3. Smoker Initial Condition*
4. At-risk Drinker Initial Condition	*4. At-risk Drinker Initial Condition*
5. Age	*5. Age*
6. Vocational Education	*6. Vocational Education*
7. Graduate Education	*7. Graduate Education*
8. Separated	*8. Separated*
9. Divorced	*9. Divorced*
10. Widowed	*10. Widowed*
11. Never married, not cohabiting	*11. Never married, not cohabiting*
12. Never married, cohabiting	*12. Never married, cohabiting*
13. Child(ren) residing at family home	*13. Child(ren) residing at family home*
14. CPI Tobacco	*14. CPI Tobacco*
15. CPI Alcohol	*15. CPI Alcohol*
16.ln(Annual Disposable Income)	*16.ln(Annual Disposable Income)*
17. Smoking Ban	*17. Smoking Ban*
18. Good Health	*18. Good Health*
19. Fair Health	*19. Fair Health*
20. Poor Health	*20. Poor Health*
21. Major City Residence	*21. Major City Residence*

Male Sub-sample Estimates	**Pooled Sample Estimates**
22. TA_ Vocational Education	*22. Male*
23. TA_ Graduate Education	*23. TA_ Separated*
24. TA_ Separated	*24. TA_ Divorced*
25. TA_ Divorced	*25. TA_ Widowed*
26. TA_ Widowed	*26. TA_ Never married, not cohabiting*
27. TA_ Never married, not cohabiting	*27. TA_ Never married, cohabiting*
28. TA_ Never married, cohabiting	*28. TA_Child(ren) residing at family home*
29. TA_Child(ren) residing at family home	*29. TA_ CPI Tobacco*
30. TA_ CPI Tobacco	*30. TA_ CPI Alcohol*
31. TA_ CPI Alcohol	*31. TA_ ln(Annual Disposable Income)*
32. TA_ ln(Annual Disposable Income)	*32. TA_ Smoking Ban*
33. TA_ Smoking Ban	*33. TA_ Good Health*
34. TA_ Good Health	*34. TA_ Fair Health*
35. TA_ Fair Health	*35. TA_ Poor Health*
36. TA_ Poor Health	*36. TA_ Major City Residence*
37. TA_ Major City Residence	*37. Constant*
38. Constant	
Drinking equation	**Drinking equation**
39. L .Smoker	*38. L .Smoker*
40. L. At-risk Drinker	*39. L. At-risk Drinker*
41. Smoker Initial Condition	*40. Smoker Initial Condition*
42. At-risk Drinker Initial Condition	*41. At-risk Drinker Initial Condition*
43. Age	*42. Age*
44. Vocational Education	*43. Vocational Education*

Male Sub-sample Estimates	**Pooled Sample Estimates**
45. Graduate Education	*44. Graduate Education*
46. Separated	*45. Separated*
47. Divorced	*46. Divorced*
48. Widowed	*47. Widowed*
49. Never married, not cohabiting	*48. Never married, not cohabiting*
50. Never married, cohabiting	*49. Never married, cohabiting*
51. Child(ren) residing at family home	*50. Child(ren) residing at family home*
52. CPI Tobacco	*51. CPI Tobacco*
53. CPI Alcohol	*52. CPI Alcohol*
54.ln(Annual Disposable Income)	*53.ln(Annual Disposable Income)*
55. Smoking Ban	*54. Smoking Ban*
56. Good Health	*55. Good Health*
57. Fair Health	*56. Fair Health*
58. Poor Health	*57. Poor Health*
59. Major City Residence	*58. Major City Residence*
60. TA_ Vocational Education	*59. Male*
61. TA_ Graduate Education	*60. TA_ Separated*
62. TA_ Separated	*61. TA_ Divorced*
63. TA_ Divorced	*62. TA_ Widowed*
64. TA_ Widowed	*63. TA_ Never married, not cohabiting*
65. TA_ Never married, not cohabiting	*64. TA_ Never married, cohabiting*
66. TA_ Never married, cohabiting	*65. TA_Child(ren) residing at family home*
67. TA_Child(ren) residing at family home	*66. TA_ CPI Tobacco*
68. TA_ CPI Tobacco	*67. TA_ CPI Alcohol*

Male Sub-sample Estimates	**Pooled Sample Estimates**
69. TA_ CPI Alcohol	*68. TA_ ln(Annual Disposable Income)*
70. TA_ ln(Annual Disposable Income)	*69. TA_ Smoking Ban*
71. TA_ Smoking Ban	*70. TA_ Good Health*
72. TA_ Good Health	*71. TA_ Fair Health*
73. TA_ Fair Health	*72. TA_ Poor Health*
74. TA_ Poor Health	*73. TA_ Major City Residence*
75. TA_ Major City Residence	*74. Constant*
76. Constant	
Other parameters	**Other parameters**
77. Unobserved time-variant effects correlation	*75. Unobserved time-variant effects correlation*
78. *Unobserved time-invariant effect variance, smoking equation*	76. *Unobserved time-invariant effect variance, smoking equation*
79. *Unobserved time-invariant effect variance, drinking equation*	77. *Unobserved time-invariant effect variance, drinking equation*
80. *Unobserved time-invariant effects correlation*	78. *Unobserved time-invariant effects correlation*

Table 47: Parameter covariance matrix, male estimates

Parameters	1	2	3	4	5	6	7	8	9	10	11
1	5.49E-03										
2	-3.30E-04	6.39E-03									
3	-9.71E-03	-8.77E-05	2.68E-02								
4	-1.46E-05	-3.94E-03	5.65E-05	6.80E-03							
5	4.36E-03	-1.57E-04	-1.07E-02	-1.52E-03	7.25E-02						
6	-9.07E-04	2.43E-04	2.24E-03	-5.39E-05	9.26E-05	3.90E-02					
7	-8.79E-04	2.78E-04	2.29E-03	-3.64E-05	2.07E-04	1.41E-02	5.95E-02				
8	-2.20E-06	-2.49E-04	5.61E-04	1.31E-04	9.76E-05	2.55E-04	-2.81E-04	3.50E-02			
9	-3.81E-04	-1.72E-04	9.05E-04	2.38E-05	4.72E-04	-9.33E-05	7.60E-04	1.75E-02	3.90E-02		
10	-1.31E-03	-2.40E-04	2.05E-03	2.78E-04	-9.31E-04	4.94E-04	9.35E-04	9.44E-03	1.57E-02	1.95E-01	
11	-3.46E-04	-4.04E-05	4.50E-04	2.33E-05	-2.53E-03	8.24E-04	9.75E-04	1.92E-03	1.35E-03	1.01E-04	4.44E-02
12	-4.29E-04	2.85E-05	8.38E-04	-1.86E-05	-3.08E-03	-9.44E-04	-1.01E-03	1.17E-03	8.34E-04	-1.04E-04	3.12E-02
13	3.07E-04	6.17E-05	-7.86E-04	-1.19E-04	9.83E-04	-2.78E-04	-1.78E-04	4.24E-03	3.07E-03	1.29E-03	3.98E-03
14	5.81E-04	-4.45E-04	-2.30E-03	2.41E-04	-2.69E-04	3.30E-04	4.96E-04	-2.58E-04	-2.34E-04	-1.72E-03	1.75E-03
15	2.29E-03	4.29E-04	-4.06E-03	-1.03E-04	-9.95E-03	-7.25E-03	-9.86E-03	-1.66E-03	-2.34E-03	-6.92E-04	4.01E-03
16	2.96E-05	-5.39E-05	-3.09E-05	1.89E-05	-1.27E-04	1.63E-04	-6.81E-06	2.75E-04	1.83E-04	3.79E-04	4.16E-04
17	1.81E-04	-4.48E-05	-6.60E-04	1.77E-05	-1.65E-04	-1.82E-04	-4.61E-04	-8.68E-07	-1.22E-04	-5.51E-04	4.30E-04
18	-1.49E-04	-9.43E-05	5.20E-04	6.07E-05	-1.48E-04	-3.35E-05	2.32E-04	2.49E-04	2.56E-04	4.68E-04	-1.07E-05
19	5.21E-06	-4.12E-05	-5.21E-05	3.33E-05	2.15E-04	4.56E-05	4.15E-04	1.83E-04	6.08E-04	2.74E-04	4.52E-05
20	-2.47E-04	-2.20E-04	2.28E-04	1.51E-04	3.29E-04	1.19E-04	6.72E-04	1.00E-03	1.34E-03	2.06E-04	-7.69E-05
21	1.83E-04	1.93E-04	-6.05E-04	-1.40E-04	2.52E-05	2.02E-04	7.07E-04	-3.17E-04	-6.81E-04	-1.35E-03	-1.29E-03

Parameters	1	2	3	4	5	6	7	8	9	10	11
22	1.70E-03	-2.63E-04	-4.42E-03	-5.67E-05	2.88E-04	-3.96E-02	-1.45E-02	-4.23E-04	-1.88E-05	-5.74E-04	-7.29E-04
23	2.16E-03	-4.09E-04	-5.51E-03	3.21E-05	2.47E-04	-1.43E-02	-6.08E-02	5.57E-05	-9.85E-04	-1.27E-03	-8.14E-04
24	-2.90E-03	-3.95E-04	6.84E-03	3.79E-04	6.36E-05	3.82E-04	1.35E-03	-3.60E-02	-1.93E-02	-9.50E-03	-2.51E-03
25	-1.32E-03	1.29E-04	3.18E-03	-2.03E-04	-1.32E-04	6.67E-04	-1.82E-04	-1.72E-02	-3.96E-02	-1.51E-02	-1.90E-03
26	8.50E-05	-4.32E-04	2.41E-03	3.84E-04	-1.09E-02	-3.06E-04	-8.03E-04	-9.97E-03	-1.68E-02	-2.09E-01	-3.55E-04
27	-1.32E-03	-9.16E-05	4.32E-03	1.37E-04	1.68E-02	-5.86E-04	-8.43E-04	-1.78E-03	-1.11E-03	2.85E-04	-4.57E-02
28	-5.17E-04	4.75E-05	7.53E-04	-1.95E-04	1.48E-02	8.13E-04	1.10E-03	-1.34E-03	-8.47E-04	2.70E-04	-3.07E-02
29	-6.41E-04	5.77E-05	1.55E-03	2.90E-04	4.63E-03	5.39E-04	5.55E-04	-4.32E-03	-3.17E-03	-1.46E-03	-4.54E-03
30	8.13E-03	-7.28E-03	-2.05E-02	-1.74E-03	1.53E-02	-2.07E-03	-3.83E-03	-3.54E-03	-4.45E-04	-1.10E-03	2.50E-04
31	-1.45E-02	7.09E-03	3.53E-02	4.06E-03	-2.06E-03	8.94E-03	1.38E-02	6.50E-03	2.39E-03	1.54E-03	-5.08E-03
32	-1.36E-05	-3.84E-05	2.75E-04	-2.16E-04	3.15E-03	-1.22E-04	6.62E-05	-1.77E-04	-1.63E-05	1.07E-05	-5.69E-04
33	-1.83E-04	1.12E-03	3.54E-04	-2.29E-04	-4.68E-04	4.26E-04	1.09E-03	6.62E-04	4.89E-04	1.79E-03	-2.18E-04
34	-1.21E-03	1.13E-04	2.46E-03	-3.45E-04	-3.99E-03	4.20E-04	2.69E-04	-6.44E-05	-5.87E-05	-2.18E-04	3.65E-07
35	-8.68E-04	6.08E-05	1.82E-03	1.04E-04	-8.93E-03	1.82E-04	-6.80E-05	1.11E-04	-3.38E-04	4.01E-05	1.23E-04
36	-7.39E-04	6.91E-04	1.10E-03	-1.60E-04	-7.22E-03	5.00E-04	-2.25E-04	-8.57E-04	-1.26E-03	-3.70E-04	5.40E-05
37	8.67E-05	6.26E-05	-1.33E-04	2.21E-04	-5.04E-05	-3.43E-04	-7.86E-04	3.80E-04	5.36E-04	1.49E-03	1.38E-03
38	6.08E-03	7.73E-04	-2.07E-02	-6.88E-04	-6.65E-02	-1.76E-03	-2.93E-03	-2.69E-03	-1.72E-03	-2.92E-03	1.93E-03
39	5.89E-04	2.75E-03	-1.52E-03	-1.88E-03	6.29E-04	1.02E-04	-4.74E-05	-2.53E-04	-2.31E-04	-3.47E-04	3.65E-05
40	-2.26E-05	3.24E-04	1.51E-05	-2.05E-04	-1.54E-05	1.81E-05	2.46E-05	-1.27E-05	-1.85E-05	-6.99E-06	2.02E-05
41	-4.33E-04	-2.11E-03	1.36E-03	1.41E-03	-3.42E-04	-9.10E-05	1.75E-05	1.89E-04	1.71E-04	1.99E-04	-5.48E-05
42	2.83E-05	-5.68E-04	-1.98E-05	6.09E-04	-9.55E-05	-2.22E-05	-2.64E-05	2.92E-05	3.99E-05	9.02E-05	-4.60E-05
43	-4.18E-06	1.70E-04	1.24E-04	-2.47E-04	3.53E-03	-6.14E-06	2.98E-05	-3.28E-05	-2.74E-05	-3.16E-04	-1.16E-04
44	-3.18E-05	-2.89E-04	1.13E-04	2.14E-04	-7.06E-05	1.84E-03	6.45E-04	3.34E-05	3.53E-05	8.81E-05	4.10E-05

Parameters	1	2	3	4	5	6	7	8	9	10	11
45	-2.29E-05	-2.63E-04	1.01E-04	1.85E-04	5.05E-08	6.15E-04	2.82E-03	4.64E-05	5.86E-06	6.94E-05	4.51E-05
46	5.92E-06	2.17E-04	-4.60E-05	-1.45E-04	1.04E-05	2.35E-05	1.25E-05	1.22E-03	5.52E-04	1.87E-04	8.07E-05
47	-5.36E-06	-1.15E-04	2.32E-05	7.82E-05	-1.67E-05	1.49E-05	-9.11E-06	5.73E-04	1.21E-03	2.91E-04	4.44E-05
48	4.46E-06	-6.45E-05	-2.49E-05	9.30E-05	-1.01E-04	2.03E-05	2.43E-05	2.31E-04	3.34E-04	4.54E-03	-1.20E-05
49	2.79E-05	-7.68E-06	-9.00E-05	8.61E-06	-7.98E-05	2.71E-05	4.17E-05	7.82E-05	4.41E-05	-3.07E-05	1.64E-03
50	2.08E-05	2.38E-05	-6.86E-05	-6.76E-06	-9.36E-05	-4.30E-05	-1.82E-05	4.35E-05	2.52E-05	-2.02E-05	1.01E-03
51	1.27E-05	6.55E-05	-3.26E-05	-4.44E-05	5.02E-05	-4.29E-06	-1.47E-06	1.29E-04	7.29E-05	1.35E-06	1.41E-04
52	2.43E-05	1.47E-05	-7.20E-05	-1.31E-05	-2.03E-05	3.43E-06	5.19E-06	1.89E-06	1.48E-06	-2.03E-06	3.18E-06
53	6.87E-05	4.31E-04	-1.99E-04	-2.62E-04	-4.92E-04	-1.54E-04	-2.59E-04	-5.32E-05	-6.82E-05	-2.50E-04	2.46E-04
54	-2.40E-06	1.35E-05	4.37E-06	-8.86E-06	-8.53E-06	3.45E-06	-5.95E-06	1.43E-05	3.81E-06	4.25E-06	1.66E-05
55	6.56E-06	-8.46E-07	-1.33E-05	3.59E-07	-2.96E-05	-8.23E-06	-1.11E-05	-6.82E-06	-3.86E-06	-1.03E-05	7.95E-06
56	1.46E-06	5.56E-06	-1.01E-05	-5.15E-06	1.11E-05	1.22E-06	3.33E-07	1.57E-06	2.12E-06	-3.55E-06	9.51E-07
57	2.36E-06	-7.92E-07	-1.28E-05	-3.96E-06	1.66E-05	5.91E-06	6.74E-06	1.25E-06	8.90E-06	-1.26E-05	9.52E-07
58	-1.95E-07	-8.41E-06	-1.46E-05	3.45E-06	2.05E-05	1.02E-05	1.97E-05	8.29E-06	1.55E-05	-4.10E-06	-5.20E-07
59	2.10E-05	-9.73E-06	-5.99E-05	5.17E-06	4.31E-05	-1.91E-05	2.90E-05	-1.65E-06	-1.17E-05	-4.05E-05	-3.54E-05
60	4.83E-05	3.24E-04	-1.36E-04	-2.65E-04	4.35E-05	-1.84E-03	-6.49E-04	-3.22E-05	-4.14E-05	-1.36E-04	-3.58E-05
61	1.91E-05	3.36E-04	-6.14E-05	-2.41E-04	-8.00E-05	-5.97E-04	-2.84E-03	-5.66E-05	-1.07E-05	-7.52E-05	-7.20E-06
62	-6.92E-05	-9.09E-04	2.12E-04	6.24E-04	5.08E-05	-6.10E-05	9.59E-07	-1.20E-03	-5.33E-04	-7.90E-05	-1.18E-04
63	-3.15E-05	-8.07E-06	2.79E-06	-2.04E-05	1.29E-04	1.06E-05	2.81E-05	-5.43E-04	-1.19E-03	-3.20E-04	-6.32E-05
64	5.89E-05	-4.63E-04	-3.15E-05	3.23E-04	-4.49E-04	-5.05E-05	-5.27E-05	-1.75E-04	-2.74E-04	-4.11E-03	-1.40E-05
65	-7.73E-05	-3.16E-04	2.38E-04	2.10E-04	8.94E-04	-3.31E-05	-5.67E-05	-5.72E-05	-2.66E-05	-4.20E-05	-1.71E-03
66	-6.39E-05	-1.14E-04	1.05E-04	4.02E-05	8.57E-04	-1.27E-05	9.65E-06	-5.00E-05	-2.90E-05	-4.30E-05	-9.98E-04
67	-2.45E-05	-1.43E-04	5.77E-05	1.22E-04	3.15E-04	8.71E-07	8.01E-06	-1.30E-04	-7.55E-05	-2.35E-06	-1.65E-04

Parameters	1	2	3	4	5	6	7	8	9	10	11
68	4.23E-04	-2.08E-03	-2.76E-04	1.23E-03	7.96E-05	9.26E-04	2.64E-04	6.17E-04	4.25E-04	5.88E-04	-1.90E-04
69	-6.97E-04	1.21E-03	1.05E-03	-6.02E-04	3.18E-04	-8.76E-04	-8.62E-06	-6.45E-04	-4.97E-04	4.77E-04	2.53E-05
70	-1.06E-05	3.65E-06	3.62E-05	-3.47E-05	2.37E-04	8.51E-06	9.76E-06	-1.92E-05	-4.07E-06	-1.45E-04	-3.40E-05
71	-4.79E-05	2.50E-04	4.01E-05	-1.54E-04	5.52E-05	-8.91E-05	-3.73E-06	-2.62E-05	6.00E-06	-5.37E-05	2.68E-05
72	-2.56E-05	-8.29E-05	1.48E-05	8.12E-05	-3.14E-04	1.82E-05	1.26E-05	1.79E-05	2.26E-05	8.76E-05	-1.83E-05
73	-2.74E-05	-3.23E-05	3.52E-05	4.32E-05	-3.99E-04	2.18E-05	1.25E-05	9.45E-06	-1.24E-06	-1.43E-05	-1.28E-05
74	-1.09E-04	1.33E-04	1.58E-04	-8.65E-05	-4.15E-04	3.64E-05	1.49E-05	-2.44E-06	-1.53E-05	-1.03E-04	1.66E-05
75	-7.50E-06	1.63E-04	4.21E-06	-1.12E-04	-5.34E-05	9.62E-06	-3.28E-05	-5.12E-06	-3.56E-06	2.12E-06	3.55E-05
76	3.23E-04	4.32E-04	-1.08E-03	9.81E-06	-4.24E-03	-1.85E-05	-5.56E-05	1.21E-04	1.34E-04	8.12E-04	2.04E-04
77	-5.36E-05	1.40E-03	-1.36E-04	-8.72E-04	6.33E-05	1.17E-04	-4.80E-05	-1.34E-04	-1.26E-04	-2.19E-04	-5.48E-06
78	-3.96E-03	-1.28E-04	1.08E-02	3.78E-04	-5.21E-03	1.00E-03	1.12E-03	1.53E-04	3.76E-04	7.08E-04	2.54E-04
79	-1.10E-05	-3.50E-04	7.50E-05	2.26E-04	-2.70E-05	-2.81E-05	-1.52E-05	2.74E-05	3.18E-05	4.06E-06	-3.40E-05
80	-1.13E-04	-3.33E-03	7.30E-04	2.32E-03	-4.10E-04	-1.97E-04	-5.09E-05	2.96E-04	2.50E-04	4.67E-04	-6.27E-05

Parameters	12	13	14	15	16	17	18	19	20	21	22
12	3.53E-02										
13	2.39E-03	1.04E-02									
14	1.01E-03	1.04E-04	6.74E-02								
15	3.78E-03	5.02E-04	-1.39E-01	4.40E-01							
16	7.06E-05	-2.40E-04	1.80E-04	-1.41E-03	1.06E-03						
17	3.72E-04	-5.52E-05	4.22E-03	-2.77E-02	-4.28E-05	4.65E-03					
18	-1.38E-04	-7.79E-05	-1.68E-04	5.11E-04	-3.69E-07	-1.08E-04	3.99E-03				

Parameters	12	13	14	15	16	17	18	19	20	21	22
19	-2.17E-04	-9.12E-05	-5.31E-05	-7.87E-04	2.42E-05	-2.17E-05	3.28E-03	9.11E-03			
20	-1.29E-04	-4.67E-05	-8.53E-04	8.50E-04	7.57E-05	-3.11E-04	3.16E-03	7.30E-03	3.10E-02		
21	-1.10E-03	2.23E-04	2.53E-04	3.94E-04	2.71E-05	6.90E-05	-4.87E-05	-3.11E-04	-5.74E-04	2.35E-02	
22	1.07E-03	3.62E-04	-1.01E-04	7.72E-03	-1.39E-04	2.35E-04	-2.80E-05	-7.62E-05	-1.91E-04	-2.26E-04	4.46E-02
23	1.09E-03	2.13E-04	-8.18E-05	1.05E-02	3.45E-05	5.68E-04	-3.09E-04	-3.92E-04	-8.16E-04	-4.62E-04	1.72E-02
24	-1.69E-03	-4.58E-03	-3.99E-04	-3.95E-04	-2.82E-04	-2.27E-04	7.22E-06	-1.32E-04	-9.68E-04	1.02E-04	-1.07E-03
25	-1.37E-03	-3.16E-03	-2.83E-04	1.22E-03	-1.83E-04	-4.14E-05	-1.90E-04	-6.18E-04	-1.33E-03	4.75E-04	-1.09E-03
26	7.50E-05	-1.85E-03	1.58E-03	1.76E-03	-3.82E-04	5.03E-04	-3.68E-04	-2.97E-04	-3.57E-04	1.08E-03	7.01E-04
27	-3.24E-02	-4.12E-03	-2.55E-03	-7.17E-03	-4.33E-04	-6.77E-04	1.74E-04	3.07E-05	2.30E-04	1.24E-03	7.86E-04
28	-3.51E-02	-2.71E-03	-1.45E-03	-6.31E-03	-8.91E-05	-4.93E-04	1.73E-04	1.52E-04	7.02E-05	7.70E-04	-1.07E-03
29	-2.92E-03	-1.07E-02	-2.52E-04	-1.51E-03	2.57E-04	-6.39E-05	1.16E-04	1.02E-04	7.15E-05	-3.38E-04	-8.48E-04
30	6.37E-04	1.51E-03	-7.68E-02	1.76E-01	-5.31E-04	-4.72E-03	2.15E-04	1.38E-03	1.31E-03	5.59E-03	1.28E-03
31	-3.52E-03	-3.67E-03	1.47E-01	-4.97E-01	1.77E-03	3.08E-02	1.96E-04	-2.13E-04	3.94E-05	-5.02E-03	-7.93E-03
32	-2.31E-04	3.09E-04	-2.73E-04	8.26E-04	-1.14E-03	3.67E-05	-1.08E-05	-4.22E-05	-1.44E-04	-1.02E-04	-1.31E-04
33	2.13E-04	-1.77E-04	-6.73E-03	3.66E-02	1.55E-04	-5.82E-03	4.42E-05	-1.12E-04	5.61E-04	-8.05E-04	-6.25E-04
34	4.21E-05	-5.29E-05	-1.76E-04	-2.26E-04	-2.65E-05	-2.25E-05	-4.00E-03	-3.33E-03	-3.17E-03	-1.02E-04	-6.49E-04
35	3.14E-04	1.05E-04	8.10E-05	1.68E-03	-1.42E-05	-8.81E-07	-3.19E-03	-9.26E-03	-7.23E-03	4.44E-04	-7.74E-05
36	5.22E-05	9.67E-05	9.02E-04	-4.22E-04	-1.57E-04	2.80E-04	-3.09E-03	-7.29E-03	-3.26E-02	3.48E-04	-6.21E-04
37	1.19E-03	-1.30E-04	-1.80E-04	-2.87E-04	-4.03E-05	-6.38E-05	7.60E-05	3.48E-04	6.07E-04	-2.37E-02	2.49E-04
38	8.60E-04	1.13E-03	6.28E-03	2.52E-02	8.01E-04	-1.50E-03	-1.03E-03	-2.91E-04	-1.14E-03	-6.99E-06	2.33E-03
39	2.24E-05	2.53E-05	-1.23E-04	3.94E-04	-2.25E-05	1.21E-05	-5.93E-05	-1.85E-05	-1.44E-04	9.37E-05	1.04E-05
40	1.47E-05	-1.66E-06	-2.12E-05	1.43E-08	9.62E-07	-3.42E-06	-1.95E-06	-4.05E-06	4.96E-06	1.06E-05	-3.42E-05
41	-3.79E-05	-2.31E-05	8.87E-05	-3.15E-04	1.66E-05	-8.17E-06	4.51E-05	1.43E-05	9.62E-05	-8.12E-05	2.87E-05

Parameters	12	13	14	15	16	17	18	19	20	21	22
42	-3.13E-05	1.78E-06	3.46E-05	1.21E-05	-3.77E-06	6.64E-06	3.19E-06	4.37E-06	-1.01E-05	-2.15E-05	3.61E-05
43	-1.18E-04	4.17E-05	-7.64E-05	-5.70E-04	-8.86E-08	-3.70E-05	8.35E-07	-5.94E-07	-8.73E-06	2.06E-05	-3.91E-05
44	-3.59E-05	-9.80E-06	4.36E-05	-2.35E-04	5.26E-06	-8.87E-06	1.21E-05	1.23E-05	3.84E-05	-2.56E-05	-1.85E-03
45	-1.92E-05	1.86E-06	2.24E-05	-2.87E-04	-2.64E-06	-1.11E-05	1.15E-05	1.26E-05	3.92E-05	4.10E-05	-6.31E-04
46	5.03E-05	1.33E-04	-1.85E-05	3.30E-05	1.30E-05	-8.22E-06	-1.90E-07	1.91E-06	-3.28E-06	3.07E-06	-1.58E-05
47	2.91E-05	7.46E-05	1.75E-05	-4.27E-05	5.01E-06	-1.97E-06	4.70E-06	9.82E-06	2.18E-05	-1.44E-05	-1.34E-05
48	-1.21E-05	1.44E-05	-1.16E-05	-1.01E-04	6.01E-06	-1.16E-05	4.43E-06	2.56E-06	7.09E-06	-2.27E-05	-3.88E-05
49	1.02E-03	1.41E-04	1.31E-05	2.46E-04	1.76E-05	1.09E-05	-7.08E-07	1.84E-06	-5.12E-06	-2.71E-05	-1.68E-05
50	1.22E-03	8.08E-05	1.18E-05	2.16E-04	3.15E-06	7.30E-06	-2.47E-06	-1.63E-06	-1.78E-07	-1.37E-05	5.06E-05
51	8.45E-05	3.37E-04	-5.49E-08	5.27E-06	-8.51E-06	5.18E-07	-6.23E-08	3.38E-06	3.51E-06	-8.25E-06	1.24E-06
52	6.33E-06	7.31E-06	1.89E-03	-3.97E-03	3.08E-06	1.25E-04	-6.33E-06	-2.95E-06	-8.18E-06	-1.44E-06	-7.21E-07
53	2.06E-04	-1.86E-06	-4.01E-03	1.29E-02	-4.23E-05	-8.16E-04	-1.65E-05	-4.35E-05	-9.55E-05	8.42E-05	1.78E-04
54	2.86E-06	-8.39E-06	1.00E-06	-3.64E-05	3.59E-05	-1.81E-06	-5.71E-07	3.81E-07	1.48E-06	-5.16E-06	-3.83E-06
55	5.10E-06	6.54E-07	1.23E-04	-8.13E-04	-1.67E-06	1.38E-04	-9.52E-07	-1.29E-06	-3.12E-06	-1.36E-06	1.07E-05
56	-2.74E-06	1.88E-07	-2.49E-06	-7.28E-06	-4.80E-07	-4.88E-07	1.25E-04	1.06E-04	1.02E-04	-1.79E-06	1.00E-06
57	-3.37E-06	4.12E-06	3.65E-06	-4.64E-05	2.27E-07	-1.04E-06	1.06E-04	2.97E-04	2.49E-04	-5.50E-06	-3.02E-06
58	-2.29E-07	7.76E-06	1.06E-05	-9.26E-05	2.64E-06	-2.55E-06	1.05E-04	2.52E-04	1.05E-03	-4.04E-06	-1.71E-05
59	-2.25E-05	-6.28E-06	3.32E-06	7.03E-05	-5.36E-06	3.19E-08	-4.04E-06	-5.14E-06	-7.02E-06	7.92E-04	2.43E-05
60	4.38E-05	8.80E-06	-4.01E-05	2.36E-04	-4.76E-06	1.02E-05	-1.12E-05	-1.13E-05	-4.68E-05	2.64E-05	2.10E-03
61	5.61E-05	-2.34E-06	-1.83E-05	2.79E-04	2.57E-06	1.00E-05	-1.10E-05	-1.16E-05	-4.33E-05	-2.91E-05	7.38E-04
62	-8.66E-05	-1.20E-04	5.16E-05	-1.32E-04	-1.03E-05	1.11E-05	1.49E-05	4.23E-06	2.49E-05	-2.45E-05	4.34E-05
63	-5.34E-05	-6.80E-05	-1.27E-05	-8.24E-06	1.51E-06	-2.43E-06	-6.06E-06	-5.14E-06	-5.59E-06	1.31E-05	-4.84E-05
64	-7.70E-06	-1.63E-05	5.78E-05	2.36E-04	-1.97E-05	2.60E-05	6.18E-07	1.14E-05	-1.53E-06	1.57E-06	7.92E-05

Parameters	12	13	14	15	16	17	18	19	20	21	22
65	-1.08E-03	-1.34E-04	-1.86E-05	-4.18E-04	-1.60E-05	-1.42E-05	-3.05E-08	-4.18E-06	1.34E-05	1.91E-05	4.71E-05
66	-1.21E-03	-8.93E-05	4.71E-06	-4.33E-04	4.58E-07	-1.50E-05	1.13E-05	5.68E-06	1.10E-05	1.21E-06	-2.03E-05
67	-1.05E-04	-3.41E-04	-3.40E-06	-5.08E-05	9.91E-06	-7.15E-06	1.20E-07	-3.78E-06	-2.52E-07	2.70E-06	-4.21E-06
68	-2.14E-04	-2.40E-05	-1.98E-03	4.54E-03	-5.25E-05	2.00E-06	6.51E-05	1.53E-04	6.32E-05	2.04E-04	-6.29E-04
69	1.28E-04	-3.08E-05	4.05E-03	-1.39E-02	9.53E-05	7.63E-04	-5.12E-06	-7.18E-05	9.29E-05	-3.94E-04	6.62E-04
70	-1.89E-05	1.10E-05	-1.03E-05	-5.58E-06	-3.78E-05	-1.13E-06	-1.43E-07	-4.49E-06	-9.74E-06	5.30E-06	-1.49E-05
71	5.82E-05	-2.54E-06	-2.36E-04	1.11E-03	9.45E-06	-1.84E-04	-1.23E-05	-2.49E-05	-1.10E-05	2.42E-06	1.96E-05
72	-1.19E-05	4.78E-07	7.33E-06	4.69E-05	-1.57E-06	1.72E-06	-1.26E-04	-1.07E-04	-9.80E-05	-1.50E-05	-6.74E-06
73	-6.45E-06	-1.23E-05	1.39E-05	6.50E-05	9.88E-07	5.61E-06	-1.04E-04	-3.07E-04	-2.48E-04	1.29E-06	-1.14E-05
74	1.08E-05	-1.46E-05	-3.04E-05	9.82E-05	-4.23E-06	1.39E-06	-1.03E-04	-2.53E-04	-1.13E-03	2.36E-05	-2.39E-06
75	2.47E-05	1.16E-05	-1.30E-05	-4.43E-05	5.99E-06	-1.26E-06	1.91E-06	5.70E-06	7.23E-06	-7.94E-04	-2.96E-05
76	1.23E-04	5.45E-06	2.65E-04	1.06E-03	1.77E-05	-1.58E-05	-3.41E-05	3.77E-06	4.91E-05	1.15E-04	-1.44E-04
77	-1.06E-05	-1.61E-05	-2.11E-04	2.89E-04	-6.33E-06	-1.09E-05	-1.04E-05	-2.86E-05	-1.24E-04	4.30E-05	-1.10E-04
78	4.04E-04	-2.98E-04	-9.64E-04	-1.70E-03	5.90E-06	-2.89E-04	1.99E-04	-6.76E-05	7.62E-05	-2.98E-04	-1.93E-03
79	-2.65E-05	2.21E-06	1.60E-05	-2.21E-05	-8.35E-07	2.85E-06	3.34E-06	2.00E-06	-5.80E-06	-1.38E-05	4.92E-05
80	-7.04E-05	-8.21E-06	1.62E-04	-1.18E-04	2.72E-05	1.17E-05	5.45E-05	8.05E-06	1.26E-04	-7.46E-05	1.48E-04

Parameters	23	24	25	26	27	28	29	30	31	32	33
23	6.99E-02										
24	-2.69E-03	7.63E-02									
25	9.64E-05	2.15E-02	5.36E-02								

Parameters	23	24	25	26	27	28	29	30	31	32	33
26	1.36E-03	1.47E-02	1.99E-02	2.83E-01							
27	6.38E-04	8.25E-03	6.25E-03	2.46E-03	5.99E-02						
28	-1.62E-03	6.32E-03	4.85E-03	4.68E-04	3.71E-02	5.17E-02					
29	-7.58E-04	7.17E-03	5.58E-03	3.44E-03	9.75E-03	5.67E-03	1.80E-02				
30	7.95E-03	8.43E-03	-1.48E-03	2.71E-03	-1.37E-04	-2.79E-03	-6.00E-03	4.71E+00			
31	-2.27E-02	-9.32E-03	1.21E-03	-1.73E-03	1.50E-02	6.15E-03	1.20E-02	-4.99E+00	6.76E+00		
32	-8.27E-04	9.08E-04	8.46E-04	1.62E-03	1.65E-03	8.88E-04	-1.04E-03	-3.55E-03	2.67E-04	3.82E-03	
33	-7.69E-04	-1.81E-03	-1.22E-03	-1.41E-03	-6.33E-05	-2.12E-03	3.30E-04	-5.06E-01	3.44E-01	-9.68E-05	1.15E-01
34	1.44E-04	1.51E-03	1.02E-03	1.10E-03	6.60E-04	6.49E-04	-3.22E-04	-6.43E-03	8.68E-03	2.40E-04	2.15E-04
35	4.94E-04	-7.06E-04	4.59E-04	9.49E-04	-5.72E-04	-3.79E-04	-8.35E-04	4.74E-03	-6.96E-03	7.37E-04	-7.05E-04
36	5.99E-04	2.57E-03	2.59E-03	2.26E-03	5.25E-04	7.40E-04	-2.21E-04	1.26E-02	-1.67E-02	1.73E-03	-1.85E-03
37	2.08E-05	-1.16E-05	-5.53E-04	-1.53E-03	-2.00E-03	-9.60E-04	4.27E-04	-1.28E-02	8.33E-03	-2.63E-04	2.69E-03
38	1.41E-02	-1.26E-02	-1.27E-02	-1.81E-02	-3.49E-02	-1.42E-02	-3.17E-03	1.94E-01	-1.51E+00	-2.72E-02	1.34E-01
39	7.41E-05	-3.67E-	-3.31E-	-1.80E-04	-2.90E-04	-3.45E-05	3.88E-05	-3.72E-03	2.87E-03	9.61E-06	7.44E-04

Parameters	23	24	25	26	27	28	29	30	31	32	33
		04	05								
40	-4.57E-05	-4.21E-05	1.51E-05	-5.50E-05	-4.80E-05	-8.70E-06	2.03E-06	-3.76E-04	3.15E-04	-6.08E-06	5.54E-05
41	8.33E-06	2.05E-04	-1.26E-05	1.96E-04	2.53E-04	-3.63E-06	-3.51E-05	2.94E-03	-2.24E-03	1.91E-05	-5.88E-04
42	5.78E-05	1.01E-04	-4.01E-05	7.27E-05	1.18E-04	5.53E-06	1.85E-05	4.07E-04	-2.67E-04	-5.42E-06	-7.43E-05
43	-1.03E-04	1.76E-04	1.81E-04	-4.00E-04	9.99E-04	9.01E-04	3.57E-04	-3.49E-04	1.23E-03	2.28E-04	1.07E-04
44	-6.40E-04	1.93E-05	1.13E-05	-1.51E-05	-2.52E-05	8.93E-06	6.48E-06	1.05E-03	-8.23E-04	3.46E-06	-1.57E-04
45	-2.85E-03	1.91E-05	2.59E-05	-2.18E-05	-5.29E-05	1.04E-05	2.37E-06	6.19E-04	-3.02E-04	5.06E-06	-8.86E-05
46	-1.54E-05	-1.29E-03	-5.43E-04	-2.21E-04	-9.60E-05	-5.63E-05	-1.34E-04	1.14E-05	-4.98E-05	-1.41E-05	3.54E-05
47	1.47E-05	-5.92E-04	-1.20E-03	-2.50E-04	-4.02E-05	-3.71E-05	-8.43E-05	5.33E-04	-5.76E-04	2.35E-07	-5.59E-05
48	-1.67E-05	-2.20E-04	-3.77E-04	-4.42E-03	-3.96E-05	-1.71E-05	-2.98E-05	3.02E-04	6.08E-05	-5.54E-05	-1.99E-05
49	-3.28E-06	-1.27E-04	-7.82E-05	1.14E-05	-1.71E-03	-1.02E-03	-1.67E-04	3.57E-05	-2.21E-04	-3.21E-05	5.26E-06
50	4.37E-05	-8.76E-05	-5.96E-05	1.32E-05	-1.07E-03	-1.22E-03	-1.00E-04	-2.16E-04	8.74E-05	-1.63E-05	6.84E-05

Parameters	23	24	25	26	27	28	29	30	31	32	33
51	7.57E-07	-1.33E-04	-7.48E-05	-2.28E-05	-1.41E-04	-8.72E-05	-3.39E-04	-3.36E-04	3.14E-04	1.12E-05	3.91E-05
52	7.60E-06	-2.58E-05	-1.77E-05	8.16E-06	-3.16E-05	-1.24E-05	-1.12E-05	-2.67E-03	4.77E-03	-9.70E-06	-1.46E-04
53	2.57E-04	-6.12E-05	9.88E-06	2.54E-04	-3.96E-04	-3.52E-04	-5.74E-05	5.20E-03	-1.51E-02	1.55E-05	1.15E-03
54	4.67E-06	-1.40E-05	-2.47E-07	-1.19E-05	-1.77E-05	-3.19E-06	8.82E-06	-3.33E-05	7.02E-05	-3.81E-05	6.27E-06
55	1.33E-05	5.81E-06	2.06E-07	2.17E-05	-1.55E-05	-1.19E-05	-4.16E-06	-1.24E-04	9.28E-04	-1.29E-06	-1.76E-04
56	2.10E-06	-3.29E-06	-5.27E-06	-4.57E-07	-4.48E-06	5.03E-06	-1.01E-06	6.52E-06	1.76E-05	9.41E-07	-1.17E-06
57	-2.88E-06	3.56E-06	-6.76E-06	1.21E-05	7.70E-07	6.40E-06	-3.53E-06	3.41E-05	1.52E-05	-7.32E-07	-8.41E-07
58	-1.97E-05	-1.16E-05	-1.74E-05	-4.21E-06	-3.55E-06	3.21E-07	-4.93E-06	5.05E-05	9.99E-06	-6.73E-06	-2.00E-06
59	-6.71E-06	-1.91E-05	1.38E-06	3.14E-05	3.12E-05	7.86E-06	1.11E-06	3.46E-04	-4.79E-04	2.52E-06	-1.81E-05
60	7.72E-04	-3.66E-05	-4.30E-05	2.74E-05	4.63E-05	-3.89E-05	-8.39E-06	-8.33E-04	7.36E-04	-1.10E-05	9.76E-05
61	3.18E-03	-3.45E-05	-1.16E-05	3.83E-05	3.24E-05	-5.53E-05	7.20E-06	-9.39E-05	-4.69E-04	-4.33E-05	4.48E-05
62	-1.29E-05	3.32E-03	6.35E-04	4.51E-04	3.88E-04	2.62E-04	1.89E-04	9.66E-04	-7.56E-04	7.28E-05	-2.20E-04

Parameters	23	24	25	26	27	28	29	30	31	32	33
63	-2.20E-05	6.60E-04	1.89E-03	3.55E-04	2.51E-04	2.20E-04	1.88E-04	-3.66E-04	1.25E-04	4.99E-05	-1.12E-05
64	1.07E-04	4.05E-04	3.80E-04	6.81E-03	8.43E-05	-3.99E-05	4.11E-05	1.38E-03	-1.41E-03	7.01E-05	-2.14E-04
65	2.88E-05	3.79E-04	2.70E-04	1.07E-04	2.52E-03	1.30E-03	4.02E-04	3.63E-04	8.33E-05	1.10E-04	-4.95E-06
66	-5.05E-05	3.02E-04	2.38E-04	-9.69E-06	1.30E-03	2.18E-03	2.46E-04	-6.45E-04	9.25E-04	5.76E-05	-1.57E-04
67	-2.82E-06	2.37E-04	1.93E-04	7.70E-05	4.16E-04	2.41E-04	6.99E-04	4.26E-04	-2.53E-04	-5.60E-05	-3.19E-05
68	6.16E-04	-5.38E-04	-4.95E-04	4.57E-04	2.30E-04	-7.97E-04	-7.61E-05	2.65E-01	-2.81E-01	-2.02E-04	-2.91E-02
69	-1.21E-03	8.42E-04	3.94E-04	-6.56E-04	2.13E-04	9.68E-04	2.64E-04	-2.81E-01	3.66E-01	-3.39E-05	2.13E-02
70	-4.69E-05	8.23E-05	6.07E-05	1.02E-04	1.16E-04	6.57E-05	-5.42E-05	-2.89E-04	9.46E-05	2.04E-04	2.04E-06
71	-8.39E-05	1.83E-05	-3.35E-05	-1.06E-04	5.22E-05	-1.07E-04	4.18E-05	-2.86E-02	2.10E-02	-8.72E-06	6.00E-03
72	3.16E-05	5.75E-05	2.18E-05	9.82E-05	1.28E-05	-2.15E-07	-5.26E-05	1.06E-04	8.12E-05	7.18E-06	-3.52E-05
73	4.21E-05	-3.78E-05	-1.45E-05	-9.75E-06	-4.20E-05	-3.75E-05	-4.53E-05	6.58E-04	-6.90E-04	5.00E-05	-9.71E-05
74	3.90E-06	1.15E-04	1.04E-04	1.31E-04	2.16E-05	6.56E-06	3.28E-05	4.57E-04	-1.05E-03	5.66E-05	8.87E-05
75	-2.44E-05	-5.35E-06	-1.27E-05	-7.16E-05	-8.03E-05	-1.50E-05	4.98E-06	-9.92E-04	8.14E-04	-1.45E-05	1.62E-04
76	6.93E-04	-1.24E-	-6.96E-	-1.05E-03	-1.94E-03	-9.85E-04	1.25E-07	1.37E-02	-8.00E-02	-1.65E-03	6.85E-03

Parameters	23	24	25	26	27	28	29	30	31	32	33
		03	04								
77	6.39E-06	-2.82E-05	9.91E-05	1.07E-06	-2.95E-05	3.95E-05	5.72E-05	-1.49E-03	1.35E-03	2.08E-06	2.59E-04
78	-2.63E-03	3.32E-03	1.57E-03	8.42E-04	1.76E-03	5.75E-04	6.78E-04	-8.57E-03	1.45E-02	5.42E-06	2.24E-04
79	3.05E-05	6.83E-05	-2.73E-06	6.24E-05	9.40E-05	2.60E-05	-2.51E-06	3.60E-04	-2.65E-04	1.56E-05	-6.02E-05
80	1.29E-04	1.69E-04	-1.44E-04	1.73E-04	1.64E-04	-6.95E-05	-1.14E-04	6.79E-03	-6.32E-03	-3.26E-05	-1.14E-03

Parameters	34	35	36	37	38	39	40	41	42	43	44
34	1.32E-02										
35	5.80E-03	2.55E-02									
36	8.72E-03	5.69E-03	8.57E-02								
37	1.41E-04	-3.77E-04	-8.83E-05	2.76E-02							
38	-7.89E-03	-7.52E-03	-1.51E-02	6.46E-03	1.74E+00						
39	2.47E-06	-8.26E-05	2.77E-04	6.75E-05	9.41E-04	7.49E-03					
40	1.26E-05	2.56E-05	8.71E-07	3.21E-06	1.35E-04	-1.37E-04	2.68E-03				
41	-6.57E-05	4.04E-06	-2.41E-04	-4.34E-05	-1.11E-03	-5.46E-03	-3.38E-04	8.05E-03			
42	-1.08E-05	-3.03E-05	9.11E-06	-4.16E-06	-1.05E-04	8.95E-05	-3.50E-03	2.40E-04	1.05E-02		
43	-2.73E-04	-3.65E-04	-2.77E-04	-4.99E-05	-4.62E-03	9.48E-04	1.69E-04	1.33E-03	-2.03E-03	6.19E-02	
44	1.59E-05	1.88E-05	-2.97E-05	-6.64E-06	-1.43E-04	-4.96E-04	1.79E-04	3.45E-04	-2.59E-04	6.32E-04	3.10E-02

Parameters	34	35	36	37	38	39	40	41	42	43	44
45	1.26E-06	5.77E-06	-4.81E-05	-6.04E-05	-1.24E-04	-5.37E-04	3.10E-04	2.97E-04	-4.72E-04	1.29E-03	8.66E-03
46	1.17E-05	-2.43E-06	4.43E-05	1.48E-05	2.20E-05	2.64E-04	-1.70E-04	-1.06E-04	1.47E-04	2.07E-04	2.57E-04
47	5.26E-06	-1.87E-05	-2.34E-05	3.09E-06	1.77E-05	-2.37E-04	-2.87E-04	1.78E-04	5.18E-04	2.98E-04	-4.86E-05
48	3.26E-05	-1.28E-05	-5.87E-05	2.04E-05	3.16E-04	-3.96E-04	2.34E-04	1.31E-04	-3.89E-04	1.53E-04	4.26E-04
49	-2.24E-05	-1.87E-05	8.61E-07	3.00E-05	1.81E-04	-1.24E-04	7.29E-06	-4.64E-05	2.40E-05	-2.05E-03	5.43E-04
50	-1.47E-05	-8.94E-06	-1.06E-05	1.80E-05	1.18E-04	9.61E-06	4.70E-05	-1.45E-04	-1.28E-04	-2.48E-03	-9.88E-04
51	-5.93E-07	-1.26E-05	-2.37E-06	1.37E-05	-1.86E-05	2.54E-04	1.32E-06	-2.27E-04	-4.98E-05	6.48E-04	-7.35E-05
52	5.82E-06	-6.82E-06	1.72E-05	6.89E-06	1.73E-04	1.33E-06	-4.77E-05	-1.02E-04	-1.48E-04	-9.47E-04	2.58E-04
53	5.92E-05	1.28E-04	1.83E-04	-5.38E-05	1.41E-03	1.14E-03	-5.78E-04	-8.66E-04	1.41E-03	-1.08E-02	-4.82E-03
54	2.60E-06	2.34E-06	-4.06E-07	6.17E-06	2.05E-05	2.81E-05	3.76E-06	-5.34E-05	-3.49E-05	-1.75E-04	4.46E-05
55	-1.22E-06	2.39E-06	2.48E-06	4.53E-07	-5.05E-05	4.89E-05	-3.05E-05	-2.81E-05	1.03E-04	-4.38E-04	-6.33E-05
56	-1.30E-04	-1.07E-04	-9.84E-05	2.63E-06	-2.03E-05	-3.02E-05	-5.36E-05	4.39E-05	1.10E-04	8.65E-05	-1.00E-04
57	-1.09E-04	-3.04E-04	-2.47E-04	6.02E-06	-4.90E-06	-2.95E-05	-1.15E-04	5.61E-05	2.01E-04	7.64E-05	1.34E-05
58	-1.07E-04	-2.63E-04	-1.11E-03	5.38E-06	7.26E-05	-2.38E-04	1.56E-04	1.06E-04	-6.12E-04	2.90E-04	1.03E-04
59	-1.60E-05	-5.71E-06	1.23E-05	-8.00E-04	1.11E-04	-9.49E-05	6.80E-05	5.11E-05	5.43E-05	-2.80E-06	-1.39E-04
60	-4.09E-06	-4.01E-06	8.42E-05	-9.60E-06	-7.48E-06	6.66E-04	-1.72E-04	-3.73E-04	1.40E-04	-1.03E-03	-3.12E-02
61	5.69E-05	6.17E-05	1.13E-04	1.52E-05	6.86E-04	8.27E-04	-2.51E-04	-1.16E-04	3.46E-04	-2.28E-03	-8.56E-03
62	1.77E-05	-3.78E-05	-5.77E-05	-2.88E-05	-1.05E-03	-1.32E-03	-6.46E-04	1.19E-04	1.81E-03	3.84E-03	-3.98E-04
63	2.48E-05	-9.07E-06	5.56E-05	-2.87E-05	-4.28E-04	-1.72E-04	1.19E-04	-5.10E-04	-3.86E-04	3.14E-03	1.30E-04
64	5.77E-05	-2.78E-05	2.95E-05	-5.70E-05	-7.16E-04	-9.00E-05	-1.16E-03	8.03E-04	2.46E-03	-7.71E-03	-5.24E-04
65	3.62E-06	-3.95E-05	-2.33E-05	-7.67E-05	-1.84E-03	-4.37E-04	-3.29E-04	5.39E-04	7.08E-04	1.84E-02	-7.50E-04
66	-5.42E-06	-4.01E-05	-1.60E-05	-1.68E-05	-9.95E-04	-2.91E-04	-9.35E-05	-4.60E-04	9.05E-05	1.52E-02	8.04E-04
67	-5.08E-05	-3.99E-05	-2.50E-06	-5.56E-06	3.98E-06	-3.59E-04	3.88E-06	1.16E-04	2.81E-04	6.08E-03	2.19E-04

Parameters	34	35	36	37	38	39	40	41	42	43	44
68	-1.27E-04	3.96E-04	7.84E-04	-7.71E-04	1.32E-02	3.65E-03	-8.59E-03	2.29E-03	1.84E-02	4.33E-03	2.47E-03
69	3.04E-04	-4.43E-04	-1.60E-03	6.44E-04	-7.96E-02	-7.43E-03	1.02E-02	8.73E-04	-2.18E-02	1.36E-02	1.57E-03
70	2.88E-06	4.98E-05	6.53E-05	-1.59E-05	-1.67E-03	4.14E-05	-2.00E-04	2.85E-04	2.46E-04	3.60E-03	-7.37E-05
71	9.82E-06	-4.06E-05	6.20E-05	1.13E-04	6.86E-03	-1.08E-04	9.02E-04	-6.94E-04	-1.95E-03	5.49E-04	-4.96E-05
72	5.64E-04	2.38E-04	3.29E-04	2.86E-05	-4.01E-04	-3.41E-04	-5.99E-05	-5.93E-04	-4.74E-05	-2.41E-03	1.19E-04
73	2.38E-04	1.14E-03	1.36E-04	-9.10E-06	-5.91E-04	-1.93E-04	5.97E-05	-5.71E-04	-7.62E-05	-6.28E-03	4.58E-05
74	3.74E-04	1.72E-04	4.41E-03	4.86E-05	-2.06E-04	1.46E-05	6.35E-05	-1.40E-03	3.31E-04	-4.77E-03	3.64E-04
75	3.54E-05	-1.10E-08	6.19E-05	9.99E-04	2.63E-04	2.46E-04	1.62E-04	-2.49E-04	-4.15E-04	-4.02E-04	1.24E-04
76	-3.71E-04	-5.87E-04	-2.05E-04	2.30E-04	9.10E-02	1.39E-03	2.59E-03	-6.22E-03	-4.05E-03	-7.78E-02	6.66E-04
77	3.53E-05	2.26E-05	2.56E-04	1.53E-05	3.31E-05	1.72E-03	1.55E-05	-1.26E-03	-1.11E-04	1.76E-04	-3.14E-04
78	1.35E-03	1.12E-03	1.04E-03	-1.12E-05	-7.48E-03	-6.95E-04	-3.64E-06	5.17E-04	3.62E-05	-1.57E-05	5.88E-05
79	-1.52E-05	-2.34E-05	1.95E-05	-3.49E-06	-2.81E-04	-9.31E-05	-1.86E-03	6.10E-04	4.40E-03	-4.05E-04	-2.15E-04
80	-1.14E-04	4.66E-05	-4.44E-04	-1.01E-04	-3.68E-04	-3.46E-03	-1.71E-04	2.66E-03	4.34E-04	-1.79E-04	3.32E-04

Parameters	45	46	47	48	49	50	51	52	53	54	55
45	5.30E-02										
46	-2.50E-04	2.49E-02									
47	3.88E-04	1.13E-02	2.70E-02								
48	5.52E-04	3.89E-03	6.44E-03	7.08E-02							
49	9.94E-04	1.24E-03	8.72E-04	-2.65E-04	3.24E-02						
50	-3.42E-04	7.83E-04	5.74E-04	-2.99E-04	2.25E-02	2.66E-02					
51	-1.05E-04	2.57E-03	1.85E-03	1.96E-04	2.90E-03	1.88E-03	7.38E-03				

Parameters	45	46	47	48	49	50	51	52	53	54	55
52	4.40E-04	3.60E-04	-1.19E-04	-2.28E-04	3.02E-04	1.70E-04	1.43E-04	3.97E-02			
53	-5.94E-03	-1.70E-03	-6.87E-04	-2.50E-03	4.32E-03	3.53E-03	8.14E-05	-8.39E-02	2.71E-01		
54	-1.47E-04	3.24E-04	1.33E-04	4.23E-04	3.01E-04	2.41E-05	-1.55E-04	1.95E-04	-1.08E-03	8.19E-04	
55	-1.92E-04	-2.63E-05	-1.00E-04	-3.03E-04	2.78E-04	2.19E-04	5.70E-06	2.59E-03	-1.72E-02	-3.61E-05	2.90E-03
56	-5.55E-05	3.56E-05	8.20E-05	1.64E-04	-1.04E-04	-2.18E-04	6.53E-06	-2.88E-04	4.71E-04	-1.24E-05	-6.09E-05
57	6.02E-05	-3.82E-06	2.37E-04	1.53E-04	-1.38E-04	-2.38E-04	-3.83E-05	-2.67E-04	-2.66E-04	9.53E-06	-3.17E-05
58	1.77E-04	1.68E-04	1.58E-04	3.10E-04	-3.24E-04	-3.30E-04	-2.62E-04	-1.46E-04	-6.69E-04	5.85E-05	-1.76E-04
59	9.07E-05	-1.69E-04	-7.50E-04	4.77E-04	-6.83E-04	-5.02E-04	-2.28E-04	-9.05E-05	1.25E-03	-8.89E-05	5.19E-06
60	-8.78E-03	-2.87E-04	-5.86E-07	-4.56E-04	-4.53E-04	1.09E-03	7.80E-05	-2.42E-04	4.96E-03	-2.58E-05	6.27E-05
61	-5.37E-02	1.66E-04	-4.44E-04	-5.70E-04	-8.34E-04	4.74E-04	5.03E-05	-4.38E-04	6.23E-03	1.90E-04	1.92E-04
62	5.15E-04	-2.57E-02	-1.21E-02	-4.13E-03	-1.62E-03	-1.27E-03	-2.54E-03	-3.49E-04	8.99E-04	-3.54E-04	3.87E-05
63	-2.75E-04	-1.10E-02	-2.72E-02	-6.46E-03	-1.23E-03	-1.02E-03	-1.78E-03	-1.04E-04	4.17E-04	-1.42E-04	7.06E-05
64	-6.99E-04	-3.98E-03	-6.66E-03	-7.39E-02	2.40E-04	3.19E-04	-3.71E-04	1.30E-04	4.25E-03	-4.46E-04	4.05E-04
65	-1.32E-03	-1.23E-03	-8.22E-04	2.21E-04	-3.33E-02	-2.34E-02	-2.81E-03	-6.34E-04	-6.66E-03	-3.48E-04	-3.82E-04
66	2.68E-04	-9.27E-04	-6.31E-04	2.81E-04	-2.23E-02	-2.64E-02	-1.93E-03	-4.92E-04	-5.48E-03	-8.48E-05	-2.66E-04
67	3.76E-04	-2.58E-03	-1.92E-03	-2.86E-04	-3.29E-03	-2.31E-03	-7.47E-03	-1.99E-04	-1.23E-03	1.42E-04	-7.94E-05
68	3.24E-04	-1.44E-03	-3.53E-04	-4.15E-03	-3.85E-04	-1.14E-03	-1.38E-03	-5.02E-02	1.07E-01	-4.31E-04	-2.42E-03
69	4.96E-03	2.73E-03	5.38E-05	5.99E-03	-3.29E-03	-8.22E-04	1.25E-04	9.53E-02	-3.11E-01	1.41E-03	1.92E-02
70	1.94E-04	-2.57E-04	1.19E-06	-3.23E-04	-3.96E-04	-1.27E-04	2.41E-04	-3.00E-04	6.38E-04	-9.10E-04	3.13E-05
71	4.88E-04	4.57E-04	2.96E-04	1.17E-03	1.07E-04	5.08E-04	2.26E-05	-3.86E-03	2.29E-02	1.14E-04	-3.78E-03
72	1.33E-04	-1.29E-05	-3.58E-05	-1.83E-04	6.63E-05	1.38E-04	-4.36E-05	3.09E-04	4.72E-05	1.03E-05	5.92E-05
73	3.67E-06	-5.15E-05	-3.33E-04	-1.94E-04	2.87E-04	3.61E-04	3.09E-05	3.89E-04	1.43E-03	-2.91E-05	8.11E-05
74	1.54E-05	-7.14E-05	-1.44E-04	-3.49E-04	4.33E-04	3.83E-04	3.99E-04	2.14E-04	1.22E-03	-9.95E-05	2.05E-04

Parameters	45	46	47	48	49	50	51	52	53	54	55
75	-3.81E-05	2.27E-04	6.81E-04	-2.95E-04	7.58E-04	5.63E-04	2.57E-04	1.42E-04	-1.26E-03	8.94E-05	-2.25E-05
76	-8.50E-04	-9.28E-04	-5.06E-04	7.58E-05	1.12E-03	6.28E-04	6.72E-05	2.66E-03	2.25E-02	9.91E-04	-1.72E-03
77	-2.14E-04	1.67E-04	-7.23E-05	-1.64E-05	1.71E-05	9.11E-06	5.47E-05	-2.39E-06	3.23E-04	1.54E-05	8.26E-06
78	5.68E-05	-2.25E-05	1.63E-05	5.61E-07	-3.56E-05	-2.79E-05	-1.35E-05	-3.33E-05	-7.98E-05	2.51E-06	-4.85E-06
79	-2.14E-04	8.36E-05	3.48E-04	-2.93E-04	-6.93E-05	-1.53E-04	-3.62E-05	-1.31E-04	6.86E-04	-2.37E-05	4.78E-05
80	3.40E-04	-2.66E-04	1.07E-04	7.13E-05	1.31E-05	-3.38E-05	-7.79E-05	-2.11E-05	-5.91E-04	-1.31E-05	1.58E-06

Parameters	56	57	58	59	60	61	62	63	64	65	66
56	2.59E-03										
57	2.18E-03	6.26E-03									
58	2.11E-03	5.05E-03	2.38E-02								
59	-3.56E-05	-1.39E-05	1.64E-04	1.66E-02							
60	8.08E-05	-4.27E-05	-9.83E-05	1.58E-04	3.55E-02						
61	5.63E-05	-5.63E-05	-2.05E-04	6.01E-08	1.10E-02	6.08E-02					
62	4.41E-06	9.00E-05	-2.34E-04	2.81E-04	3.24E-04	-7.98E-04	6.15E-02				
63	-7.65E-05	-2.18E-04	-2.36E-04	7.53E-04	-2.80E-04	5.84E-04	1.28E-02	4.04E-02			
64	-1.19E-04	-1.12E-04	-5.03E-04	-5.04E-04	8.38E-04	7.16E-04	7.36E-03	8.98E-03	1.18E-01		
65	1.39E-04	1.73E-04	3.18E-04	7.60E-04	1.42E-03	1.81E-03	5.80E-03	4.79E-03	1.24E-03	4.65E-02	
66	1.92E-04	1.90E-04	1.72E-04	4.34E-04	-8.47E-04	-4.76E-04	4.96E-03	4.09E-03	-7.61E-05	2.77E-02	4.35E-02
67	-3.16E-06	2.61E-05	2.58E-04	2.26E-04	-3.35E-04	-3.44E-04	4.33E-03	3.88E-03	1.12E-03	7.66E-03	4.64E-03
68	1.34E-03	2.25E-03	-1.63E-03	3.28E-03	-5.51E-03	1.39E-03	1.46E-02	2.08E-03	1.75E-02	9.10E-03	-9.65E-04
69	-1.45E-03	-2.15E-03	2.77E-03	-3.81E-03	2.12E-03	-1.03E-02	-1.80E-02	-2.12E-03	-2.21E-02	7.33E-04	2.22E-04

Parameters	56	57	58	59	60	61	62	63	64	65	66
70	2.24E-05	1.03E-05	-9.84E-05	8.16E-05	-1.76E-04	-1.04E-03	1.25E-03	6.90E-04	2.15E-03	1.59E-03	9.14E-04
71	-5.64E-05	-1.11E-04	5.84E-04	-4.37E-04	4.11E-04	1.30E-04	-1.97E-03	-1.03E-03	-1.60E-03	-2.67E-04	-2.04E-03
72	-2.64E-03	-2.21E-03	-2.15E-03	4.29E-06	-9.75E-05	5.93E-04	6.08E-04	4.72E-04	8.99E-04	4.88E-05	2.00E-04
73	-2.14E-03	-6.36E-03	-5.03E-03	3.20E-05	2.58E-04	9.18E-04	-7.99E-04	1.48E-04	7.64E-04	-9.23E-04	-7.56E-04
74	-2.08E-03	-5.04E-03	-2.40E-02	-8.05E-05	-4.05E-04	3.01E-04	5.42E-04	4.04E-04	2.59E-03	-6.65E-04	1.43E-04
75	3.54E-05	-8.31E-06	-1.16E-04	-1.68E-02	-2.70E-04	-5.53E-04	-2.56E-04	-8.58E-04	-2.47E-04	-1.43E-03	-5.33E-04
76	-3.42E-04	8.05E-05	2.44E-04	-6.40E-04	-1.05E-03	1.09E-02	-1.23E-02	-1.02E-02	-1.90E-02	-3.10E-02	-1.13E-02
77	8.59E-06	-1.46E-05	-4.93E-05	-3.94E-06	3.44E-04	2.71E-04	-4.94E-04	-1.91E-05	-1.72E-04	-1.98E-04	-6.87E-05
78	-5.76E-06	-7.06E-06	-9.83E-06	-2.43E-05	-7.41E-05	-5.74E-05	1.50E-04	7.93E-06	-2.58E-06	1.04E-04	5.66E-05
79	6.25E-05	1.14E-04	-3.48E-04	8.04E-06	1.94E-04	8.37E-05	1.09E-03	-6.06E-05	1.53E-03	5.54E-04	2.88E-04
80	-9.27E-06	-1.46E-05	1.75E-05	2.07E-05	-3.57E-04	-4.42E-04	1.08E-03	5.41E-05	4.97E-04	3.95E-04	1.47E-04

Parameters	67	68	69	70	71	72	73	74	75	76	77
67	1.39E-02										
68	2.19E-03	4.42E+00									
69	3.10E-03	-4.71E+00	6.33E+00								
70	-9.56E-04	-3.38E-03	-7.51E-04	3.80E-03							
71	8.96E-05	-4.65E-01	3.26E-01	-9.59E-05	1.02E-01						
72	-2.79E-	-4.26E-03	7.08E-03	2.73E-04	-9.98E-	1.07E-02					

Parameters	67	68	69	70	71	72	73	74	75	76	77
	04				06						
73	-6.04E-04	6.33E-03	-8.57E-03	8.23E-04	-5.54E-04	4.00E-03	2.08E-02				
74	-9.57E-04	1.31E-02	-1.68E-02	1.62E-03	-1.27E-03	6.76E-03	2.91E-03	7.65E-02			
75	-1.08E-04	-7.30E-03	5.21E-03	-4.74E-04	1.45E-03	4.56E-05	9.64E-05	2.26E-04	2.03E-02		
76	-1.96E-03	2.20E-01	-1.45E+00	-2.88E-02	1.24E-01	-8.70E-03	-7.85E-03	-1.50E-02	6.48E-03	1.65E+00	
77	-9.96E-05	5.17E-05	-8.82E-04	-3.97E-06	3.13E-05	-6.99E-05	-3.18E-05	3.84E-05	6.62E-05	3.71E-04	2.05E-03
78	3.17E-05	1.32E-04	1.68E-04	6.39E-06	-2.58E-06	3.25E-05	4.48E-05	9.59E-05	-5.47E-06	-3.17E-04	-8.41E-05
79	6.48E-05	1.15E-02	-1.38E-02	2.91E-04	-1.19E-03	9.69E-05	-6.68E-05	1.33E-04	-3.29E-04	-3.62E-03	-8.98E-05
80	1.68E-04	1.91E-03	-8.46E-04	9.44E-06	-2.26E-04	9.45E-05	5.42E-05	-1.36E-04	-1.92E-04	-5.72E-04	-1.41E-03

Parameters	78	79	80
78	5.14E-03		
79	5.03E-05	2.94E-03	
80	4.22E-04	3.44E-04	4.32E-03

Table 48: Parameter covariance matrix, female (pooled) estimates

Parameters	1	2	3	4	5	6	7	8	9	10	11
1	2.86E-03										
2	-1.37E-04	3.68E-03									
3	-4.96E-03	-6.76E-05	1.35E-02								
4	-5.97E-05	-2.18E-03	6.92E-05	3.84E-03							
5	2.23E-03	-6.50E-05	-5.37E-03	-6.21E-04	3.73E-02						
6	1.34E-04	3.85E-05	-3.70E-04	-6.03E-05	2.43E-04	1.92E-03					
7	4.68E-04	-4.97E-05	-1.16E-03	-3.45E-05	2.85E-04	8.62E-04	3.11E-03				
8	-1.97E-04	-5.05E-05	6.65E-04	3.57E-05	-1.43E-04	1.36E-07	-4.33E-05	1.68E-02			
9	-1.37E-04	-5.68E-05	3.19E-04	-1.71E-05	2.71E-04	2.27E-05	1.85E-05	8.63E-03	1.87E-02		
10	-3.94E-04	-4.49E-05	9.50E-04	1.09E-04	-5.80E-04	3.18E-05	1.39E-05	5.13E-03	6.76E-03	4.47E-02	
11	-2.07E-04	-1.64E-04	4.96E-04	1.59E-04	-1.82E-03	1.66E-04	2.31E-04	6.06E-04	3.02E-04	-5.51E-05	2.53E-02
12	-2.45E-04	-5.00E-05	6.51E-04	7.50E-05	-1.85E-03	6.65E-05	5.34E-05	4.53E-04	2.30E-04	-9.07E-05	1.78E-02
13	1.00E-04	1.68E-05	-2.50E-04	-3.60E-05	1.63E-04	3.63E-05	5.10E-05	1.35E-03	1.08E-03	3.93E-04	1.59E-03
14	4.11E-04	-8.20E-05	-1.12E-03	2.57E-05	-2.19E-04	3.81E-05	1.53E-04	-2.93E-05	1.05E-04	-6.33E-04	6.78E-04
15	7.03E-04	1.42E-04	-1.74E-03	-7.09E-05	-4.98E-03	-3.73E-04	-3.73E-04	-1.11E-03	-1.81E-03	-1.29E-03	2.93E-03
16	-3.00E-06	-2.30E-05	5.06E-05	1.21E-05	-8.60E-05	5.24E-06	-1.04E-05	1.97E-04	1.28E-04	3.65E-04	2.24E-04
17	1.30E-04	-2.44E-05	-3.82E-04	5.20E-06	-7.21E-05	4.73E-07	3.37E-05	-2.46E-05	-8.71E-05	-3.17E-04	1.83E-04
18	-7.08E-05	-2.62E-05	2.50E-04	2.21E-05	-1.10E-04	-1.05E-05	-1.45E-05	1.67E-04	4.22E-05	2.06E-04	5.41E-05
19	-2.52E-06	-3.10E-05	-1.66E-04	2.13E-05	1.14E-04	7.39E-06	3.91E-05	1.64E-04	1.59E-04	2.10E-04	9.18E-05
20	5.28E-05	-8.87E-05	-4.75E-04	3.97E-05	3.40E-04	1.78E-05	3.38E-05	2.93E-04	2.69E-04	-3.73E-05	5.39E-05
21	2.30E-04	1.00E-04	-6.17E-04	-1.11E-04	1.92E-04	7.96E-07	1.52E-04	-3.09E-04	-3.92E-04	-3.12E-04	-4.87E-04

Parameters	1	2	3	4	5	6	7	8	9	10	11
22	-2.71E-04	-1.67E-04	7.08E-04	-1.10E-04	-6.31E-04	-2.32E-04	-1.01E-04	1.60E-05	-4.55E-05	-9.76E-07	-6.33E-06
23	-1.19E-03	-1.19E-04	2.84E-03	1.39E-04	-9.93E-05	-2.56E-04	-5.22E-04	-1.73E-02	-9.41E-03	-5.22E-03	-7.67E-04
24	-6.35E-04	-1.99E-05	1.51E-03	5.63E-05	-5.11E-04	-2.27E-04	-3.19E-04	-8.45E-03	-1.89E-02	-6.71E-03	-5.42E-04
25	-1.86E-04	7.41E-05	7.95E-04	-3.03E-06	-4.96E-03	9.73E-05	-7.50E-05	-5.14E-03	-6.88E-03	-4.64E-02	8.40E-05
26	-6.10E-04	8.69E-05	1.77E-03	-2.69E-05	8.88E-03	-7.34E-05	-4.74E-04	-5.02E-04	-2.37E-04	2.08E-04	-2.59E-02
27	-3.04E-04	9.63E-05	4.35E-04	-2.30E-04	8.16E-03	-1.38E-04	-4.21E-04	-4.54E-04	-2.32E-04	1.19E-04	-1.75E-02
28	-3.55E-04	3.26E-05	8.40E-04	1.68E-04	2.10E-03	-1.22E-04	-9.75E-05	-1.40E-03	-1.17E-03	-3.69E-04	-1.93E-03
29	2.05E-05	4.59E-06	-4.63E-05	-2.62E-05	3.22E-05	-1.56E-05	5.27E-07	-7.41E-06	-2.68E-06	-2.05E-06	-3.50E-06
30	-3.39E-05	4.07E-06	8.04E-05	3.42E-05	1.58E-05	1.84E-05	-4.83E-06	2.78E-05	2.78E-05	2.87E-05	-3.05E-05
31	7.77E-05	-5.15E-05	-1.40E-04	-7.62E-05	1.72E-03	-7.45E-05	-2.61E-04	-1.57E-04	-6.77E-05	-3.17E-04	-2.81E-04
32	-1.99E-04	-1.27E-04	4.92E-04	2.31E-04	-3.15E-05	1.50E-04	1.58E-04	7.36E-05	1.43E-04	3.58E-04	1.54E-05
33	-5.28E-04	1.22E-05	1.04E-03	-8.68E-05	-1.77E-03	-7.52E-05	1.71E-04	-1.00E-04	-8.37E-06	-9.91E-05	-5.31E-05
34	-3.46E-04	6.89E-05	8.33E-04	2.04E-05	-3.51E-03	7.53E-05	1.52E-04	-6.67E-05	-1.17E-04	-3.42E-05	1.51E-05
35	-6.02E-04	3.26E-04	1.34E-03	8.75E-05	-3.54E-03	-2.96E-05	9.82E-05	-1.83E-04	-2.48E-04	7.89E-05	-4.48E-06
36	-7.22E-05	-4.21E-05	2.28E-04	1.60E-04	-1.49E-04	-8.50E-06	-3.13E-04	3.01E-04	3.15E-04	2.95E-04	4.94E-04
37	1.12E-03	-3.65E-04	-5.32E-03	-2.57E-04	-3.22E-02	3.05E-04	3.43E-03	-1.74E-03	-1.72E-03	-1.64E-03	1.09E-03
38	2.94E-04	1.67E-03	-7.41E-04	-1.09E-03	2.60E-04	4.68E-05	3.47E-05	-8.11E-05	-7.93E-05	-1.11E-04	-1.67E-05
39	-4.30E-07	1.07E-04	-1.02E-05	-6.12E-05	-7.76E-06	2.72E-06	3.54E-06	1.35E-06	2.22E-06	3.33E-06	-5.32E-06
40	-2.12E-04	-1.33E-03	6.85E-04	8.64E-04	-1.34E-04	-3.26E-05	-9.98E-06	6.08E-05	6.11E-05	8.31E-05	1.46E-05
41	-9.63E-06	-1.72E-04	1.89E-05	2.66E-04	-2.01E-05	-1.57E-05	-1.08E-05	-2.70E-06	-4.72E-06	1.87E-06	1.73E-06
42	4.15E-05	2.83E-04	-3.62E-05	-2.20E-04	1.96E-03	2.44E-05	3.80E-06	8.62E-06	-1.40E-05	-3.14E-05	-4.56E-05
43	7.40E-06	-4.61E-06	-1.14E-05	-3.65E-06	1.73E-05	1.12E-04	5.27E-05	2.09E-07	5.62E-07	7.35E-07	7.02E-06
44	1.71E-05	6.76E-05	-2.85E-05	-4.61E-05	1.17E-05	5.35E-05	1.62E-04	-6.08E-06	-6.15E-06	-3.00E-06	1.56E-05

Parameters	1	2	3	4	5	6	7	8	9	10	11
45	2.46E-06	6.98E-05	-2.00E-05	-4.48E-05	1.32E-05	3.04E-06	-1.14E-06	4.87E-04	2.38E-04	1.18E-04	1.85E-05
46	3.06E-06	1.99E-05	-1.07E-05	-1.72E-05	-7.67E-06	-2.39E-07	-3.74E-06	2.44E-04	5.22E-04	1.61E-04	9.25E-06
47	2.55E-06	2.60E-05	-1.64E-05	-9.73E-06	-1.84E-06	2.69E-06	4.39E-06	1.11E-04	1.53E-04	8.96E-04	-3.37E-06
48	-6.20E-06	-9.64E-05	1.98E-05	6.08E-05	-4.41E-05	5.74E-06	1.57E-05	1.99E-05	1.33E-05	1.46E-06	7.93E-04
49	-8.19E-06	-1.02E-04	2.54E-05	6.69E-05	-6.08E-05	-2.97E-07	8.38E-06	1.42E-05	1.10E-05	1.51E-06	5.26E-04
50	4.27E-06	2.19E-05	-9.73E-06	-1.24E-05	7.16E-06	6.08E-07	9.37E-07	3.69E-05	2.51E-05	4.10E-06	4.50E-05
51	1.73E-05	4.03E-05	-4.50E-05	-2.34E-05	-1.62E-05	1.59E-06	2.83E-06	-3.60E-06	1.80E-06	-1.01E-05	2.79E-06
52	-8.25E-06	9.84E-05	6.33E-06	-6.51E-05	-3.28E-04	-1.81E-05	-2.73E-05	-1.54E-05	-4.06E-05	-5.72E-05	9.82E-05
53	-1.45E-06	-8.08E-07	3.66E-06	1.25E-06	-5.27E-07	3.91E-07	-1.11E-06	7.73E-06	3.98E-06	9.01E-06	7.85E-06
54	3.16E-06	1.11E-05	-7.65E-06	-7.34E-06	-1.31E-05	-4.51E-07	3.33E-07	-3.52E-06	-3.23E-06	-7.23E-06	4.23E-06
55	-5.85E-06	-5.59E-06	1.24E-05	4.48E-06	-2.66E-06	-2.55E-07	-9.11E-07	2.89E-07	2.93E-08	2.69E-06	1.17E-06
56	-8.67E-06	-1.18E-05	1.77E-05	7.92E-06	-3.01E-06	9.39E-07	-6.57E-07	4.44E-06	3.37E-06	5.62E-06	2.94E-06
57	-8.27E-06	-6.61E-06	1.73E-05	6.16E-06	-9.59E-06	1.23E-06	5.60E-07	4.03E-06	1.75E-06	-5.77E-06	1.92E-06
58	7.92E-07	1.07E-05	-2.66E-06	-3.74E-06	3.86E-06	5.22E-07	1.02E-06	-8.61E-06	-8.45E-06	-1.00E-05	-5.35E-06
59	-7.59E-06	-2.86E-05	1.67E-05	3.91E-07	-1.11E-05	-1.99E-05	-1.09E-05	-5.70E-06	-6.56E-06	1.17E-06	-3.58E-06
60	-6.30E-05	-3.25E-04	1.43E-04	2.02E-04	5.45E-05	-2.14E-05	-3.31E-05	-5.11E-04	-2.52E-04	-1.12E-04	-2.77E-05
61	-4.97E-05	-7.23E-05	9.69E-05	4.51E-05	-8.01E-06	-1.85E-05	-2.15E-05	-2.22E-04	-5.14E-04	-1.53E-04	-1.41E-05
62	-6.04E-06	-1.04E-04	1.97E-05	6.19E-05	-2.34E-04	8.02E-06	2.01E-06	-1.09E-04	-1.54E-04	-9.08E-04	3.67E-06
63	-1.83E-05	-8.17E-05	4.17E-05	5.41E-05	5.01E-04	7.87E-06	-1.30E-05	5.43E-07	-6.67E-06	4.68E-06	-8.14E-04
64	-2.63E-05	-6.66E-05	4.17E-05	3.22E-05	4.12E-04	9.66E-06	-1.15E-05	5.42E-06	-3.70E-06	8.58E-06	-5.18E-04
65	-1.63E-05	-3.47E-05	2.96E-05	2.95E-05	1.12E-04	-1.43E-06	-6.33E-06	-2.36E-05	-2.15E-05	-3.65E-07	-5.85E-05
66	4.99E-07	-6.85E-07	1.73E-08	-2.60E-06	7.87E-06	-1.40E-06	-1.42E-06	1.02E-06	8.73E-07	3.86E-08	-1.19E-07
67	-1.53E-06	-1.47E-06	2.94E-06	3.22E-06	-8.70E-06	1.15E-06	1.16E-06	-2.15E-06	-1.94E-06	9.01E-07	-1.02E-06

Parameters	1	2	3	4	5	6	7	8	9	10	11
68	-3.38E-07	-2.16E-05	8.41E-06	1.56E-06	1.18E-04	-6.05E-06	-1.83E-05	-1.12E-05	-7.56E-06	-1.85E-05	-1.03E-05
69	1.31E-05	3.26E-05	-5.43E-05	3.44E-05	4.76E-05	2.82E-05	2.92E-05	2.17E-05	2.71E-05	8.57E-06	1.90E-05
70	-1.18E-05	-9.21E-05	9.66E-06	5.67E-05	-7.78E-05	-1.03E-05	1.27E-05	-4.33E-06	-4.90E-06	4.42E-07	-1.21E-06
71	-1.50E-06	-9.74E-05	-5.67E-06	7.46E-05	-1.76E-04	-3.58E-06	1.72E-05	-2.09E-06	-8.84E-06	-1.98E-06	2.61E-06
72	-7.71E-06	-1.77E-05	-2.10E-05	1.64E-05	-1.09E-04	-1.40E-07	6.64E-06	-7.69E-06	-1.20E-05	-1.94E-05	2.29E-06
73	1.01E-06	-1.39E-05	1.31E-06	1.40E-05	-6.89E-06	-3.39E-06	-1.45E-05	3.59E-06	3.40E-06	6.54E-06	8.30E-06
74	1.12E-04	3.51E-04	-4.47E-04	-2.31E-05	-1.89E-03	6.64E-05	2.23E-04	1.69E-04	2.06E-04	8.95E-05	6.21E-05
75	-4.92E-06	8.00E-04	-9.19E-05	-4.74E-04	3.43E-05	1.64E-05	-8.75E-06	-3.35E-05	-5.07E-05	-4.31E-05	2.66E-06
76	-2.04E-03	-3.49E-05	5.50E-03	2.05E-04	-2.69E-03	-1.50E-04	-5.66E-04	2.25E-04	1.10E-04	3.28E-04	2.39E-04
77	-1.42E-05	-1.37E-04	4.81E-05	8.82E-05	-5.72E-06	-9.63E-06	-5.48E-06	1.44E-06	1.01E-06	1.42E-06	-3.23E-06
78	-5.38E-05	-1.89E-03	3.00E-04	1.23E-03	-7.01E-06	-3.91E-05	1.91E-05	6.02E-05	7.61E-05	9.59E-05	-5.77E-06

Parameters	12	13	14	15	16	17	18	19	20	21	22
12	2.03E-02										
13	1.08E-03	6.14E-03									
14	2.97E-04	9.91E-05	3.63E-02								
15	2.34E-03	5.90E-04	-7.40E-02	2.33E-01							
16	2.75E-05	-1.62E-04	1.48E-05	-6.45E-04	6.01E-04						
17	1.50E-04	2.01E-05	2.17E-03	-1.46E-02	-2.51E-05	2.46E-03					
18	-5.51E-05	-2.96E-06	-1.30E-04	1.91E-04	7.14E-07	-2.38E-05	2.11E-03				
19	-4.94E-05	-2.31E-05	-1.81E-04	-6.32E-05	3.51E-06	5.11E-06	1.73E-03	4.86E-03			
20	-4.72E-05	-6.92E-05	-4.30E-04	2.53E-04	9.71E-05	-4.16E-05	1.69E-03	3.90E-03	1.59E-02		

Parameters	12	13	14	15	16	17	18	19	20	21	22
21	-4.22E-04	-2.03E-05	8.37E-05	4.53E-04	-5.63E-06	-1.85E-05	-6.15E-05	-5.22E-05	-1.06E-04	1.16E-02	
22	3.75E-05	-1.41E-04	-5.83E-05	-8.00E-05	7.01E-06	-1.16E-05	7.05E-06	-2.82E-05	-5.39E-05	2.18E-05	1.72E-03
23	-5.65E-04	-1.48E-03	-3.55E-04	5.81E-04	-1.83E-04	-8.33E-05	-9.83E-05	-2.41E-04	-4.94E-04	2.11E-04	4.10E-04
24	-4.33E-04	-1.12E-03	-3.05E-04	1.43E-03	-1.22E-04	1.54E-05	-1.05E-05	-1.95E-04	-4.06E-04	2.66E-04	4.85E-04
25	1.73E-04	-5.55E-04	6.49E-04	1.78E-03	-3.81E-04	3.08E-04	-1.81E-04	-2.90E-04	-9.14E-05	1.98E-04	8.27E-04
26	-1.85E-02	-1.72E-03	-1.07E-03	-4.49E-03	-2.21E-04	-3.09E-04	-6.57E-06	-1.07E-04	-1.20E-04	3.59E-04	1.56E-04
27	-2.01E-02	-1.18E-03	-6.03E-04	-3.51E-03	-4.41E-05	-2.31E-04	5.93E-05	-1.40E-05	-3.18E-05	3.04E-04	4.90E-05
28	-1.37E-03	-6.29E-03	-1.72E-04	-1.10E-03	1.63E-04	-7.75E-05	1.22E-05	-8.81E-06	2.03E-05	-2.93E-05	3.72E-04
29	-9.42E-06	1.66E-05	-4.20E-04	9.58E-04	-9.28E-07	-2.79E-05	-1.77E-06	4.17E-06	9.43E-06	2.54E-05	-4.12E-06
30	-8.10E-06	-3.05E-05	7.96E-04	-2.66E-03	8.12E-06	1.69E-04	1.69E-06	-1.73E-06	-7.44E-06	-3.08E-05	1.03E-05
31	-5.72E-05	2.01E-04	-4.84E-05	4.81E-04	-6.32E-04	2.40E-05	-2.61E-06	-7.60E-06	-1.03E-04	-1.20E-05	-7.54E-05
32	2.61E-04	-3.79E-04	-3.43E-03	1.88E-02	7.41E-05	-3.09E-03	8.13E-05	4.58E-05	1.64E-04	-1.34E-04	-5.28E-06
33	2.81E-05	-3.24E-05	1.84E-05	-1.24E-04	-4.46E-06	-3.36E-05	-2.12E-03	-1.76E-03	-1.77E-03	-5.30E-05	3.79E-05
34	1.17E-04	5.34E-05	2.18E-04	3.48E-04	1.77E-05	-2.17E-05	-1.68E-03	-4.88E-03	-3.80E-03	2.37E-05	2.55E-06
35	9.95E-05	7.37E-05	4.42E-04	-4.27E-04	-1.26E-04	3.53E-05	-1.66E-03	-3.92E-03	-1.65E-02	4.00E-05	1.47E-04
36	4.37E-04	4.30E-05	-4.94E-05	-3.29E-04	1.02E-06	2.75E-05	6.56E-05	5.75E-05	1.13E-04	-1.16E-02	-5.82E-05
37	-2.48E-05	6.75E-04	2.69E-03	1.27E-02	2.08E-04	-1.11E-03	-1.80E-04	1.11E-04	2.09E-04	4.62E-04	-8.43E-04
38	5.10E-06	3.15E-05	1.71E-05	1.65E-04	-1.41E-05	8.19E-06	-1.28E-05	-5.57E-06	-2.34E-05	1.01E-04	-1.17E-04
39	-6.17E-07	-1.53E-06	1.21E-07	-4.78E-07	-5.70E-07	-1.57E-07	-9.01E-07	-1.82E-06	-4.50E-07	1.84E-06	1.19E-06
40	-6.14E-06	-2.18E-05	-1.50E-05	-1.23E-04	1.10E-05	-5.70E-06	1.11E-05	4.40E-06	1.75E-05	-7.81E-05	9.12E-05
41	-1.06E-06	1.33E-06	1.08E-07	2.86E-07	7.75E-07	-1.21E-06	1.76E-06	2.21E-06	-4.91E-07	-1.57E-06	-2.02E-05
42	-4.68E-05	8.90E-06	-2.24E-05	-3.34E-04	-1.43E-06	-9.90E-06	2.17E-06	4.51E-07	-3.00E-06	1.70E-05	-2.31E-05
43	4.19E-06	-2.59E-07	-4.75E-07	-1.70E-05	-1.10E-07	4.26E-07	-9.45E-07	1.45E-06	2.30E-06	2.40E-06	-1.85E-05

Parameters	12	13	14	15	16	17	18	19	20	21	22
44	1.07E-05	1.40E-06	4.10E-06	-2.17E-05	-1.62E-06	1.77E-06	-1.28E-06	6.63E-07	1.83E-06	7.66E-06	-1.35E-05
45	1.28E-05	3.58E-05	-1.84E-06	2.28E-06	7.14E-06	-2.95E-06	-2.08E-07	2.86E-06	4.76E-07	-3.79E-06	-6.17E-06
46	7.36E-06	2.49E-05	7.59E-06	-4.10E-05	3.30E-06	-1.20E-06	-1.71E-07	2.21E-06	1.98E-06	-7.75E-06	-5.52E-06
47	-3.94E-06	2.28E-06	-4.87E-06	-5.75E-05	7.59E-06	-4.43E-06	9.64E-07	3.57E-06	-7.90E-06	-5.03E-06	-1.74E-06
48	5.28E-04	4.48E-05	6.92E-06	8.49E-05	7.22E-06	4.57E-06	7.66E-07	3.18E-06	3.26E-06	-1.39E-05	1.01E-06
49	6.38E-04	2.80E-05	7.16E-06	6.78E-05	1.38E-08	2.62E-06	-2.59E-07	-2.49E-07	2.62E-06	-8.94E-06	5.77E-06
50	3.04E-05	1.63E-04	4.97E-06	1.30E-05	-5.29E-06	1.56E-06	2.85E-07	1.32E-06	9.58E-07	-5.53E-06	-6.13E-06
51	5.97E-06	5.81E-06	8.06E-04	-1.67E-03	-7.85E-07	5.18E-05	-4.96E-06	-5.49E-06	-8.15E-06	2.54E-06	-3.08E-06
52	7.48E-05	1.25E-05	-1.69E-03	5.45E-03	-1.49E-05	-3.45E-04	2.83E-06	-5.98E-06	-1.13E-05	3.19E-05	-6.26E-06
53	7.44E-08	-5.32E-06	-1.53E-06	-1.35E-05	1.76E-05	-1.24E-06	1.25E-07	2.87E-07	-1.07E-07	-2.93E-06	8.16E-07
54	2.79E-06	1.90E-06	5.14E-05	-3.40E-04	-1.09E-06	5.79E-05	-4.48E-07	-7.56E-07	-1.44E-06	4.33E-07	-1.12E-06
55	-8.06E-07	-6.08E-09	-5.07E-06	1.28E-06	7.62E-08	-6.12E-07	5.28E-05	4.43E-05	4.29E-05	-3.28E-06	-3.76E-07
56	-1.06E-06	1.13E-06	-6.68E-06	-9.21E-06	5.03E-07	-1.18E-06	4.48E-05	1.26E-04	1.01E-04	-5.92E-06	-6.77E-07
57	-3.96E-10	1.08E-06	-6.06E-06	-2.27E-05	-4.49E-07	-1.04E-06	4.32E-05	1.01E-04	4.03E-04	-4.81E-06	1.66E-06
58	-3.93E-06	-6.55E-06	-5.34E-06	3.93E-05	-9.92E-07	-2.29E-06	-7.51E-07	-1.34E-06	-1.76E-06	3.51E-04	-2.42E-06
59	-2.21E-06	-6.30E-06	-5.31E-08	-2.00E-06	8.64E-07	-9.84E-07	-1.18E-06	-2.11E-06	-2.20E-06	-5.32E-06	1.00E-04
60	-2.42E-05	-4.35E-05	-1.10E-05	-5.10E-05	-3.90E-06	3.34E-06	2.57E-06	-2.31E-06	4.80E-06	-1.74E-05	2.13E-05
61	-1.04E-05	-2.19E-05	-1.14E-05	3.77E-06	-4.09E-06	-2.00E-07	1.97E-06	-2.69E-06	-1.60E-06	-7.86E-07	2.79E-05
62	4.17E-06	-6.91E-06	1.08E-05	1.01E-04	-7.96E-06	7.14E-06	-9.67E-07	-3.03E-06	-1.51E-06	6.53E-08	3.75E-05
63	-5.52E-04	-4.75E-05	-1.54E-05	-1.90E-04	-5.76E-06	-6.09E-06	1.28E-06	5.18E-07	6.13E-08	1.81E-06	1.01E-05
64	-6.41E-04	-2.94E-05	-1.43E-05	-1.70E-04	1.10E-06	-4.94E-06	1.71E-06	-6.97E-07	3.62E-07	-6.56E-06	1.39E-06
65	-4.35E-05	-1.66E-04	-1.88E-06	-6.04E-05	4.48E-06	-2.98E-06	1.71E-06	-1.02E-06	-6.99E-07	1.59E-06	2.94E-05
66	-9.18E-07	8.90E-07	-1.01E-05	2.17E-05	-5.40E-08	-6.75E-07	-5.32E-07	-2.64E-07	-5.21E-07	3.31E-07	3.87E-07

Parameters	12	13	14	15	16	17	18	19	20	21	22
67	7.69E-07	-1.87E-06	1.87E-05	-6.09E-05	7.70E-08	4.04E-06	6.02E-07	5.58E-07	8.06E-07	-5.60E-07	4.25E-07
68	-1.83E-06	6.01E-06	-1.45E-06	-1.94E-06	-1.67E-05	3.95E-07	-9.12E-07	-7.78E-07	-3.26E-06	3.39E-06	-7.40E-06
69	2.80E-05	-7.88E-06	-6.66E-05	4.08E-04	4.46E-06	-7.29E-05	6.69E-06	3.50E-06	1.00E-05	-6.20E-06	-1.74E-05
70	1.95E-07	-2.24E-06	2.08E-06	7.11E-06	9.50E-07	-2.03E-07	-5.51E-05	-4.52E-05	-4.32E-05	-3.53E-06	1.84E-06
71	2.35E-06	-4.47E-06	7.03E-06	4.58E-05	5.90E-07	2.60E-06	-4.40E-05	-1.28E-04	-9.46E-05	-3.70E-07	-4.69E-07
72	7.31E-06	-7.14E-06	1.00E-05	1.04E-05	-2.96E-07	3.27E-06	-4.35E-05	-1.01E-04	-4.27E-04	-8.59E-07	-5.35E-06
73	6.97E-06	3.87E-06	5.15E-06	-3.48E-05	1.73E-06	2.59E-06	1.27E-06	1.74E-06	2.35E-06	-3.54E-04	3.54E-06
74	-2.80E-05	8.15E-05	9.60E-05	4.27E-04	3.51E-06	-2.37E-05	1.82E-06	-1.57E-05	2.73E-05	-1.57E-05	-4.37E-05
75	1.19E-06	1.45E-05	-3.56E-05	1.08E-04	2.58E-06	-1.03E-05	1.85E-06	-1.31E-05	-4.65E-05	4.36E-05	-4.05E-05
76	2.97E-04	-9.16E-05	-4.53E-04	-7.66E-04	2.78E-05	-1.66E-04	9.35E-05	-9.71E-05	-2.25E-04	-2.67E-04	3.33E-04
77	-6.08E-06	6.38E-07	-2.58E-06	-8.72E-06	9.41E-07	-1.36E-06	8.54E-07	7.00E-07	3.08E-08	-3.60E-06	1.90E-06
78	-4.81E-05	-2.50E-05	1.39E-05	-1.00E-04	1.76E-05	1.97E-06	1.19E-06	2.12E-06	2.38E-05	-8.56E-05	1.00E-04

Parameters	23	24	25	26	27	28	29	30	31	32	33
23	3.44E-02										
24	1.04E-02	2.45E-02									
25	7.17E-03	8.64E-03	6.21E-02								
26	3.02E-03	2.32E-03	7.07E-04	3.26E-02							
27	2.61E-03	2.02E-03	1.98E-04	2.07E-02	2.89E-02						
28	1.96E-03	1.84E-03	9.82E-04	4.03E-03	2.69E-03	9.38E-03					
29	1.42E-05	1.99E-06	9.21E-06	6.21E-06	-1.50E-05	-3.83E-05	2.04E-04				
30	-3.23E-05	-1.89E-05	-4.20E-05	5.67E-05	2.63E-05	5.52E-05	-2.19E-04	3.07E-04			

Parameters	23	24	25	26	27	28	29	30	31	32	33
31	5.90E-04	4.78E-04	1.08E-03	8.39E-04	3.64E-04	-5.25E-04	-9.33E-06	-7.82E-06	1.91E-03		
32	-2.07E-04	-6.13E-04	-3.30E-04	1.21E-04	-6.57E-04	5.67E-04	-2.10E-03	1.34E-03	-1.69E-04	5.11E-02	
33	6.34E-04	2.73E-04	3.01E-04	3.27E-04	2.97E-04	9.94E-06	-2.76E-05	3.66E-05	4.60E-05	4.58E-05	6.57E-03
34	5.85E-05	1.43E-04	3.32E-04	-8.94E-05	-2.61E-05	-1.33E-04	-4.15E-08	-7.75E-06	3.69E-04	-1.59E-04	2.92E-03
35	1.22E-03	5.21E-04	7.33E-04	4.48E-04	2.29E-04	1.29E-04	3.43E-05	-4.16E-05	7.29E-04	-6.58E-04	4.35E-03
36	-3.07E-04	-3.43E-04	-3.71E-04	-7.00E-04	-3.33E-04	5.57E-05	-5.01E-05	3.79E-05	-1.54E-04	8.67E-04	6.57E-05
37	-6.01E-03	-5.35E-03	-6.67E-03	-1.53E-02	-5.93E-03	-2.13E-05	8.99E-04	-7.28E-03	-1.29E-02	6.19E-02	-3.09E-03
38	-1.44E-04	-7.19E-05	6.32E-05	-1.12E-04	-5.76E-05	-2.96E-05	9.39E-06	-7.70E-06	-1.75E-06	-1.24E-04	-5.69E-05
39	-8.89E-06	-8.06E-06	3.59E-06	-1.78E-06	-5.84E-06	1.49E-06	-2.70E-07	1.04E-07	-7.82E-07	2.73E-06	-5.50E-06
40	8.22E-05	3.52E-05	-5.03E-05	7.89E-05	1.35E-05	7.85E-06	-6.11E-06	5.43E-06	1.22E-05	6.93E-05	1.60E-05
41	9.73E-06	8.97E-06	-1.54E-05	1.16E-05	6.88E-06	6.63E-06	-3.00E-06	3.16E-06	-1.04E-05	4.52E-05	1.16E-05
42	8.13E-05	3.19E-05	-2.04E-04	5.04E-04	4.24E-04	1.27E-04	8.54E-06	-7.05E-06	1.13E-04	1.60E-06	-8.16E-05
43	-1.10E-05	-1.56E-05	1.14E-05	8.98E-06	8.08E-06	-1.33E-06	-1.34E-06	1.19E-06	-3.99E-06	2.40E-05	-7.65E-06
44	-2.58E-05	-1.43E-05	5.49E-06	-1.81E-05	-1.38E-05	-4.66E-06	-9.31E-07	9.06E-07	-1.76E-05	1.78E-05	1.03E-05
45	-5.23E-04	-2.32E-04	-1.22E-04	-1.75E-05	-1.12E-05	-3.07E-05	1.17E-06	-1.51E-06	-8.08E-06	3.21E-06	-5.97E-06
46	-2.63E-04	-5.26E-04	-1.66E-04	-1.54E-05	-1.22E-05	-2.45E-05	8.90E-07	-1.59E-06	-5.85E-06	1.63E-05	-8.89E-06
47	-1.20E-04	-1.61E-04	-9.16E-04	-4.20E-06	-1.30E-06	-3.67E-06	-2.93E-07	1.41E-06	-1.41E-05	4.27E-06	-2.78E-06
48	-2.21E-05	-1.39E-05	-2.25E-06	-8.08E-04	-5.17E-04	-5.76E-05	-1.11E-06	4.14E-07	-6.58E-06	1.95E-05	2.86E-06
49	-1.52E-05	-1.12E-05	2.03E-06	-5.44E-04	-6.33E-04	-4.22E-05	-1.93E-06	1.87E-06	1.11E-06	3.68E-05	2.80E-06
50	-4.16E-05	-2.29E-05	-8.31E-06	-4.66E-05	-2.73E-05	-1.65E-04	1.65E-07	-7.12E-07	6.13E-06	-4.69E-06	-2.97E-06
51	-1.29E-05	-1.08E-05	1.48E-05	-1.90E-05	-1.45E-05	-8.53E-06	-9.44E-06	1.83E-05	-1.04E-06	-8.07E-05	-2.03E-06
52	9.34E-06	3.98E-05	9.10E-05	-1.75E-04	-1.46E-04	-3.59E-05	2.03E-05	-5.98E-05	-9.87E-07	4.40E-04	2.38E-05
53	-6.03E-06	-3.92E-06	-9.89E-06	-7.42E-06	-1.28E-06	5.44E-06	-2.44E-08	9.96E-08	-1.77E-05	3.11E-06	6.94E-08

Parameters	23	24	25	26	27	28	29	30	31	32	33
54	8.34E-07	1.26E-06	8.48E-06	-8.92E-06	-4.40E-06	-3.26E-06	-4.71E-07	3.89E-06	5.19E-08	-7.65E-05	5.77E-08
55	3.42E-06	1.75E-06	-1.58E-06	1.79E-06	-2.93E-07	1.42E-06	-2.93E-07	3.71E-07	-3.37E-07	1.77E-06	-5.40E-05
56	1.28E-06	-4.96E-07	-5.34E-06	2.37E-06	-1.51E-07	1.18E-07	-2.10E-07	5.53E-07	-8.32E-07	3.90E-07	-4.36E-05
57	1.90E-06	6.98E-07	8.28E-08	2.67E-06	-2.60E-06	2.22E-06	-5.90E-07	1.10E-06	-1.36E-06	2.16E-06	-4.20E-05
58	6.38E-06	6.46E-06	8.60E-06	3.71E-06	1.38E-07	6.37E-06	3.97E-07	-6.07E-07	1.46E-06	-2.84E-06	1.14E-06
59	9.73E-06	2.52E-05	3.30E-05	8.55E-06	9.95E-08	2.74E-05	3.97E-07	8.95E-08	-6.92E-06	-1.38E-05	-8.20E-07
60	1.66E-03	3.14E-04	2.03E-04	1.65E-04	1.44E-04	6.61E-05	1.64E-06	-1.88E-06	3.47E-05	-3.19E-05	1.92E-05
61	3.13E-04	8.22E-04	2.49E-04	1.16E-04	9.64E-05	4.99E-05	-3.35E-06	3.78E-06	3.16E-05	-9.56E-06	5.23E-06
62	1.96E-04	2.41E-04	1.54E-03	4.08E-05	8.82E-06	2.81E-05	-5.34E-07	-1.16E-06	5.71E-05	-4.17E-06	2.38E-06
63	1.31E-04	1.00E-04	3.76E-05	1.20E-03	6.76E-04	1.58E-04	3.49E-06	-1.91E-06	5.29E-05	-2.26E-05	9.07E-06
64	1.28E-04	9.31E-05	5.32E-06	6.80E-04	1.16E-03	8.48E-05	4.25E-07	-8.02E-07	2.62E-05	-5.17E-05	2.17E-05
65	6.35E-05	4.88E-05	3.25E-05	1.64E-04	8.47E-05	3.29E-04	1.03E-06	-1.29E-06	-2.54E-05	1.75E-05	4.49E-07
66	2.80E-06	-2.65E-06	-1.18E-06	3.12E-06	3.10E-07	5.19E-07	1.20E-05	-1.28E-05	-8.96E-07	-1.23E-04	8.59E-07
67	-1.42E-06	3.59E-06	4.92E-07	-6.77E-07	-4.15E-07	-4.10E-07	-1.28E-05	1.73E-05	-3.17E-07	8.47E-05	-5.71E-08
68	3.78E-05	3.38E-05	5.78E-05	5.70E-05	3.21E-05	-2.64E-05	-8.77E-07	-4.16E-07	9.89E-05	5.60E-06	6.13E-06
69	-7.85E-05	-3.44E-05	-1.77E-05	-3.41E-05	-6.11E-05	1.77E-05	-1.23E-04	8.50E-05	3.95E-06	2.74E-03	-2.44E-05
70	1.12E-05	-1.55E-06	-9.90E-07	1.15E-05	1.97E-05	-3.67E-06	2.40E-08	3.34E-07	4.42E-06	-4.11E-06	3.01E-04
71	-4.01E-05	9.50E-06	-1.35E-05	-8.90E-06	-5.48E-06	-1.10E-05	6.02E-07	-1.79E-06	3.37E-05	4.16E-06	1.01E-04
72	2.59E-05	7.52E-06	8.20E-06	1.25E-05	2.52E-05	1.29E-05	4.04E-06	-4.22E-06	3.38E-05	-4.81E-05	1.77E-04
73	-1.02E-06	-9.33E-06	-1.66E-05	-1.50E-05	4.54E-06	3.85E-06	-2.44E-07	-5.65E-07	-1.19E-05	2.03E-05	-1.27E-05
74	-5.99E-04	-5.24E-04	-5.25E-04	-9.86E-04	-4.35E-04	9.37E-05	6.44E-05	-4.19E-04	-7.90E-04	3.47E-03	-2.36E-04
75	-1.76E-05	1.24E-05	4.69E-05	-2.43E-05	-8.15E-06	-1.92E-06	4.89E-06	-3.05E-06	-1.06E-05	-6.13E-05	-1.34E-05
76	1.45E-03	8.03E-04	4.12E-04	7.62E-04	3.07E-04	4.12E-04	-2.47E-05	4.05E-05	-1.00E-04	2.48E-04	5.83E-04

Parameters	23	24	25	26	27	28	29	30	31	32	33
77	1.26E-05	8.66E-06	-1.37E-05	1.31E-05	1.54E-05	-2.15E-06	-4.23E-07	9.88E-07	-8.96E-07	1.06E-07	1.33E-05
78	1.96E-05	-1.07E-05	-1.34E-04	5.78E-05	5.07E-05	-1.06E-05	-8.32E-06	3.93E-06	-1.49E-06	1.44E-04	2.18E-05

Parameters	34	35	36	37	38	39	40	41	42	43	44
34	1.23E-02										
35	3.33E-03	4.00E-02									
36	3.95E-05	-1.80E-04	1.35E-02								
37	-4.43E-03	-7.13E-03	2.35E-03	8.37E-01							
38	-3.03E-05	7.99E-05	-5.90E-05	-1.06E-05	4.58E-03						
39	3.85E-06	4.44E-06	-1.81E-06	3.76E-05	-1.30E-04	1.58E-03					
40	-5.58E-06	-1.17E-04	4.70E-05	-2.13E-04	-3.40E-03	-1.82E-04	4.79E-03				
41	6.33E-06	1.84E-07	1.07E-05	6.27E-05	1.38E-04	-2.04E-03	1.03E-04	6.10E-03			
42	-1.74E-04	-8.50E-05	-1.40E-05	-2.03E-03	6.67E-04	4.05E-04	5.44E-04	-1.78E-03	3.44E-02		
43	-2.16E-06	-1.95E-06	-5.09E-06	4.21E-05	4.06E-05	1.40E-05	-7.53E-07	-6.19E-05	8.78E-05	1.95E-03	
44	1.23E-05	8.69E-06	-1.93E-05	1.98E-04	1.32E-04	5.00E-05	7.85E-05	-1.27E-04	-8.85E-05	8.82E-04	2.69E-03
45	-8.20E-06	4.76E-06	3.25E-06	4.59E-05	5.43E-07	-4.48E-05	4.20E-05	1.39E-05	4.44E-05	8.20E-06	-6.97E-06
46	-1.66E-05	-8.56E-06	5.29E-06	1.56E-04	-2.48E-05	-7.97E-05	4.44E-05	7.64E-05	1.82E-04	-3.24E-05	-5.10E-06
47	-1.54E-05	-3.80E-06	3.65E-06	3.24E-05	-1.26E-04	8.86E-05	8.90E-05	-1.08E-04	3.52E-05	3.08E-05	4.84E-05
48	7.81E-07	-3.64E-06	1.05E-05	-1.54E-05	-1.34E-04	-1.50E-04	1.33E-04	2.56E-04	-1.20E-03	1.20E-04	2.05E-04
49	4.44E-06	-4.08E-06	6.51E-06	-6.75E-05	-1.41E-04	-3.03E-05	1.15E-04	7.03E-06	-1.24E-03	2.39E-05	8.04E-05
50	-4.07E-06	-2.94E-06	4.20E-06	3.96E-05	1.10E-04	-1.45E-05	-7.92E-05	6.87E-06	1.52E-04	1.09E-05	-6.32E-06
51	2.89E-06	9.41E-06	-1.02E-06	7.08E-05	1.14E-04	5.36E-06	-1.51E-04	-5.09E-05	-4.95E-04	8.38E-06	3.29E-05

Parameters	34	35	36	37	38	39	40	41	42	43	44
52	4.84E-05	3.32E-05	-2.88E-05	4.38E-04	2.38E-04	-2.32E-04	-2.22E-04	5.68E-04	-6.01E-03	-3.21E-04	-4.38E-04
53	-1.08E-06	-2.17E-08	3.01E-06	6.14E-06	6.24E-06	-3.01E-06	-1.99E-05	-2.05E-05	-6.40E-05	1.53E-06	3.56E-06
54	2.19E-06	3.49E-06	2.11E-07	-2.68E-05	5.31E-05	-3.61E-05	-3.78E-05	6.96E-05	-2.58E-04	-9.64E-06	-1.14E-05
55	-4.35E-05	-4.21E-05	2.59E-06	-5.80E-06	-2.43E-05	-1.95E-05	2.86E-05	5.45E-05	-8.59E-06	-1.03E-06	3.02E-06
56	-1.27E-04	-9.94E-05	4.95E-06	-2.45E-05	-3.29E-05	-5.46E-05	4.27E-05	1.09E-04	-8.73E-06	7.56E-06	1.90E-05
57	-9.88E-05	-4.00E-04	1.66E-06	-1.00E-05	-6.98E-05	8.63E-05	9.07E-07	-3.90E-04	1.63E-04	2.99E-05	2.54E-05
58	8.01E-07	4.02E-06	-3.53E-04	-1.96E-05	6.19E-05	-2.43E-06	-7.37E-05	4.28E-05	3.30E-05	-2.02E-05	1.23E-05
59	-5.31E-06	-5.94E-06	5.33E-06	-3.37E-05	-5.00E-05	-2.26E-04	4.12E-05	2.75E-04	-4.58E-04	-2.42E-04	-8.42E-05
60	-3.08E-05	-4.46E-06	1.32E-05	-4.13E-04	-5.20E-04	-4.04E-04	-5.75E-05	1.04E-03	1.61E-03	-9.20E-05	-1.82E-04
61	2.02E-05	5.02E-06	-8.51E-06	-4.41E-04	-2.30E-04	-8.93E-05	-1.49E-04	2.26E-04	7.73E-04	-1.43E-04	-1.30E-04
62	1.82E-06	5.33E-06	-1.24E-05	-4.39E-04	2.43E-06	-2.13E-04	6.79E-05	4.23E-04	-4.30E-03	1.37E-04	-1.90E-05
63	-6.31E-06	6.40E-06	-9.05E-06	-8.65E-04	-1.85E-04	-4.82E-05	9.86E-05	2.14E-04	9.74E-03	6.77E-05	-1.82E-04
64	-2.53E-06	2.41E-05	1.34E-05	-3.66E-04	-1.57E-04	7.69E-05	-3.16E-04	-3.10E-04	8.69E-03	-4.44E-05	-2.78E-04
65	-7.13E-06	1.19E-05	6.41E-06	1.33E-04	-1.86E-04	6.32E-05	-8.39E-06	2.37E-05	2.97E-03	-6.33E-05	3.16E-05
66	1.20E-06	4.05E-06	-9.30E-08	6.61E-05	1.19E-05	-1.55E-05	7.06E-06	2.67E-05	-1.03E-05	-1.15E-05	2.32E-06
67	-1.87E-06	-4.30E-06	-8.08E-07	-4.21E-04	-2.03E-05	2.48E-05	-2.30E-06	-4.72E-05	8.92E-05	1.57E-05	-1.00E-05
68	3.49E-05	3.42E-05	-1.30E-05	-7.90E-04	3.95E-05	-1.31E-04	1.62E-04	2.07E-04	1.76E-03	-8.54E-05	-3.68E-04
69	-1.25E-05	-5.28E-05	2.54E-05	3.46E-03	-1.03E-04	1.43E-04	-1.25E-04	-2.01E-04	6.78E-04	1.20E-04	2.22E-04
70	1.02E-04	1.72E-04	-8.34E-06	-1.70E-04	-2.34E-04	-2.45E-05	-2.47E-04	-2.05E-06	-1.19E-03	-2.21E-05	2.57E-04
71	5.78E-04	3.50E-05	-5.50E-07	-2.96E-04	-1.67E-04	8.69E-05	-2.49E-04	-1.59E-04	-2.81E-03	8.86E-05	2.61E-04
72	4.62E-05	1.98E-03	-6.15E-06	-4.15E-04	-1.21E-04	6.21E-05	-7.27E-04	3.14E-04	-2.44E-03	4.68E-05	1.37E-04
73	-4.65E-07	-1.13E-05	4.56E-04	1.80E-04	-3.61E-05	1.07E-04	1.83E-05	-2.22E-04	-3.01E-04	7.65E-06	-1.89E-04
74	-3.39E-04	-4.29E-04	1.82E-04	4.77E-02	-2.95E-04	1.54E-03	-2.42E-03	-2.55E-03	-3.76E-02	6.23E-05	4.39E-03

Parameters	34	35	36	37	38	39	40	41	42	43	44
75	8.50E-06	1.11E-04	-3.03E-05	-2.09E-04	1.06E-03	-1.38E-05	-8.01E-04	-1.82E-05	1.62E-04	-4.02E-06	2.99E-05
76	4.96E-04	9.25E-04	9.47E-05	-2.11E-03	-3.16E-04	-7.89E-06	2.39E-04	2.42E-05	-3.78E-05	-7.62E-06	-1.69E-05
77	1.45E-06	-3.73E-06	3.28E-06	-6.81E-05	-1.95E-05	-1.06E-03	3.62E-04	2.48E-03	-6.98E-04	-1.43E-05	-8.74E-05
78	1.11E-05	-1.37E-04	5.55E-05	3.39E-04	-2.14E-03	-1.72E-05	1.71E-03	8.57E-05	-3.44E-04	-7.51E-07	-7.92E-05

Parameters	45	46	47	48	49	50	51	52	53	54	55
45	1.34E-02										
46	6.64E-03	1.46E-02									
47	2.99E-03	4.51E-03	3.67E-02								
48	4.34E-04	2.37E-04	-1.07E-04	1.96E-02							
49	2.91E-04	1.73E-04	-1.15E-04	1.38E-02	1.63E-02						
50	1.05E-03	7.93E-04	6.01E-05	1.27E-03	9.10E-04	4.69E-03					
51	-4.45E-05	-1.21E-04	-7.88E-05	1.45E-04	1.03E-04	4.38E-05	2.32E-02				
52	-2.16E-04	-3.44E-04	-1.57E-03	2.75E-03	1.98E-03	5.36E-04	-4.86E-02	1.56E-01			
53	2.07E-04	1.10E-04	2.70E-04	1.73E-04	9.60E-06	-1.22E-04	8.58E-05	-6.14E-04	5.00E-04		
54	-5.80E-05	-9.75E-05	-1.46E-04	1.30E-04	9.26E-05	2.64E-05	1.46E-03	-9.84E-03	-2.21E-05	1.66E-03	
55	2.10E-05	-3.13E-06	4.77E-05	-1.76E-05	-6.79E-05	2.16E-05	-1.34E-04	1.50E-04	-2.89E-06	-1.25E-05	1.47E-03
56	2.52E-05	1.21E-05	8.81E-05	-2.46E-05	-5.46E-05	-2.09E-06	-1.91E-04	-4.05E-05	5.95E-06	-1.15E-05	1.21E-03
57	2.07E-04	7.41E-05	-4.88E-05	-1.05E-04	-1.16E-04	-1.26E-04	-2.17E-04	-2.03E-04	5.55E-05	-5.52E-05	1.15E-03
58	-5.29E-05	-2.99E-04	9.05E-05	-2.30E-04	-2.38E-04	-1.58E-04	-4.44E-06	5.48E-04	-2.95E-05	1.26E-05	-1.02E-05
59	8.76E-06	2.22E-05	-2.75E-05	3.68E-05	5.02E-05	-9.35E-05	-2.28E-05	1.32E-04	3.97E-06	1.16E-05	-4.14E-07
60	-1.39E-02	-7.19E-03	-3.23E-03	-5.60E-04	-4.77E-04	-1.09E-03	-2.16E-05	1.33E-04	-2.31E-04	6.72E-05	-1.61E-05

Parameters	45	46	47	48	49	50	51	52	53	54	55
61	-6.51E-03	-1.47E-02	-4.57E-03	-3.91E-04	-3.53E-04	-7.51E-04	4.22E-05	3.39E-04	-1.13E-04	9.17E-05	1.44E-05
62	-3.02E-03	-4.60E-03	-3.79E-02	1.61E-04	1.78E-04	-1.27E-04	1.12E-04	2.39E-03	-2.84E-04	1.91E-04	-4.80E-05
63	-4.42E-04	-2.38E-04	8.43E-05	-2.01E-02	-1.43E-02	-1.28E-03	-3.15E-04	-4.09E-03	-1.89E-04	-1.88E-04	2.48E-05
64	-3.52E-04	-2.18E-04	8.15E-05	-1.37E-02	-1.62E-02	-9.20E-04	-3.11E-04	-3.04E-03	-3.67E-05	-1.37E-04	4.98E-05
65	-1.10E-03	-8.72E-04	-1.10E-04	-1.50E-03	-1.12E-03	-4.77E-03	-5.61E-05	-1.13E-03	1.20E-04	-6.11E-05	-2.76E-05
66	1.68E-06	3.75E-06	-1.25E-05	-5.22E-06	-1.24E-05	1.78E-06	-2.81E-04	6.19E-04	-4.29E-07	-1.63E-05	1.44E-06
67	5.81E-06	2.60E-06	3.60E-05	-2.30E-05	6.42E-07	-1.45E-05	5.39E-04	-1.78E-03	6.78E-06	1.12E-04	-1.74E-06
68	-1.74E-04	-3.55E-05	-2.29E-04	-2.11E-04	-4.30E-05	1.69E-04	-1.46E-04	4.89E-04	-5.49E-04	1.73E-05	7.22E-06
69	1.00E-04	1.36E-04	1.94E-04	1.77E-04	3.76E-04	-1.34E-04	-2.22E-03	1.29E-02	4.65E-05	-2.13E-03	1.81E-05
70	-1.37E-05	2.02E-05	-7.40E-05	-7.47E-06	1.94E-05	-2.93E-05	1.54E-04	6.68E-05	-3.35E-06	1.16E-05	-1.50E-03
71	-2.82E-05	-4.75E-05	-1.20E-04	7.49E-05	1.00E-04	5.32E-06	2.55E-04	5.27E-04	-6.75E-06	2.79E-05	-1.19E-03
72	-1.93E-04	-3.83E-05	8.21E-05	1.19E-04	1.19E-04	1.68E-04	2.24E-04	4.33E-04	-7.53E-05	8.43E-05	-1.14E-03
73	5.73E-05	2.53E-04	-7.89E-05	2.37E-04	2.56E-04	1.58E-04	2.58E-05	-5.00E-04	2.84E-05	-1.44E-05	1.20E-05
74	-9.45E-04	-1.09E-03	-1.07E-03	7.81E-04	-1.01E-06	3.48E-04	1.50E-03	1.12E-02	4.56E-04	-9.03E-04	-7.10E-05
75	5.54E-05	-1.15E-05	1.56E-05	-6.57E-05	-8.18E-05	2.20E-05	3.86E-05	1.22E-05	1.16E-06	1.38E-05	-1.93E-06
76	-9.42E-06	-4.60E-06	-8.50E-06	1.07E-05	1.20E-05	-4.51E-06	-2.01E-05	1.00E-05	2.18E-06	-3.23E-06	5.30E-06
77	1.91E-05	8.50E-05	-6.31E-05	1.00E-04	-2.83E-05	1.42E-06	-5.16E-05	2.85E-04	-1.51E-05	3.02E-05	2.96E-05
78	-8.52E-05	-2.92E-05	-2.89E-05	1.07E-04	1.18E-04	-2.69E-05	-5.01E-05	-1.47E-04	1.26E-06	-1.55E-05	5.58E-06

Parameters	56	57	58	59	60	61	62	63	64	65	66
56	3.63E-03										
57	2.82E-03	1.45E-02									

Parameters	56	57	58	59	60	61	62	63	64	65	66
58	8.63E-06	5.69E-05	9.08E-03								
59	8.07E-06	-6.56E-05	4.61E-05	1.72E-03							
60	4.19E-06	-2.93E-04	1.37E-04	2.58E-04	3.11E-02						
61	1.47E-05	-1.15E-04	2.80E-04	3.00E-04	7.61E-03	2.05E-02					
62	-1.26E-04	-2.84E-05	-9.53E-05	6.46E-04	4.62E-03	5.95E-03	5.25E-02				
63	5.06E-05	8.66E-05	2.24E-04	-5.16E-06	2.48E-03	1.92E-03	3.79E-04	2.68E-02			
64	3.56E-05	8.47E-05	2.06E-04	-5.66E-05	2.28E-03	1.82E-03	-6.05E-05	1.67E-02	2.58E-02		
65	-3.89E-06	1.17E-04	1.65E-04	2.09E-04	1.33E-03	1.38E-03	3.65E-04	3.48E-03	2.48E-03	7.81E-03	
66	6.93E-06	2.72E-06	1.26E-05	3.54E-06	3.19E-05	3.47E-06	2.81E-05	2.79E-05	-1.59E-05	-4.80E-06	2.01E-04
67	-5.77E-06	5.11E-06	-1.97E-05	-2.32E-06	-5.78E-05	-1.54E-05	-7.46E-05	2.37E-05	1.83E-05	2.50E-05	-2.18E-04
68	-4.37E-06	-7.87E-05	3.83E-05	-2.07E-05	8.80E-04	4.68E-04	1.13E-03	8.87E-04	3.92E-04	-5.30E-04	-1.78E-05
69	-1.23E-06	1.14E-04	-6.94E-05	-7.80E-05	-5.02E-04	-5.96E-04	-4.00E-05	-2.44E-05	-6.58E-04	2.66E-04	-2.03E-03
70	-1.24E-03	-1.18E-03	1.67E-05	-1.98E-05	1.77E-04	5.39E-05	9.37E-05	4.64E-05	1.30E-04	-9.19E-05	-1.74E-05
71	-3.70E-03	-2.74E-03	-1.06E-06	-1.07E-04	-3.60E-04	-1.16E-04	2.75E-04	-3.76E-04	-2.83E-04	-1.75E-04	1.83E-05
72	-2.82E-03	-1.41E-02	5.75E-05	-7.94E-05	6.23E-04	-6.07E-05	6.93E-04	-1.89E-04	4.09E-05	-2.99E-04	3.43E-05
73	-2.12E-05	-3.65E-05	-9.15E-03	-6.56E-05	-2.47E-04	-3.13E-04	-1.16E-04	-5.41E-04	-2.52E-04	-1.15E-04	-2.43E-05
74	2.28E-05	1.09E-05	1.87E-06	-9.94E-04	-6.88E-03	-4.56E-03	-6.63E-03	-1.56E-02	-5.85E-03	3.66E-04	1.34E-03
75	-1.67E-05	-2.09E-05	1.61E-05	-1.01E-05	-1.84E-04	-3.93E-05	-5.03E-05	-3.55E-05	-5.20E-06	-4.04E-05	1.28E-06
76	8.20E-06	8.36E-06	2.91E-07	8.88E-06	7.59E-05	4.76E-05	3.21E-06	1.65E-05	3.12E-05	1.58E-05	-3.83E-07
77	5.91E-05	-2.19E-04	1.90E-05	2.94E-04	5.92E-04	1.35E-04	2.32E-04	1.66E-04	-1.38E-05	-6.47E-05	2.21E-05
78	8.36E-06	1.57E-05	-1.62E-05	2.75E-05	3.88E-04	7.49E-05	1.11E-04	9.77E-05	8.45E-05	3.78E-05	-3.47E-07

Parameters	67	68	69	70	71	72	73	74	75	76	77
67	3.05E-04										
68	-7.09E-06	2.04E-03									
69	1.32E-03	2.13E-06	4.80E-02								
70	3.27E-05	1.29E-04	-1.62E-04	5.75E-03							
71	-3.21E-05	4.53E-04	-1.28E-04	2.09E-03	1.15E-02						
72	-4.98E-05	7.52E-04	-4.68E-04	3.52E-03	1.45E-03	4.39E-02					
73	1.86E-05	-2.38E-04	5.48E-04	1.27E-05	7.77E-05	-4.56E-06	1.10E-02				
74	-7.71E-03	-1.47E-02	6.05E-02	-4.33E-03	-4.00E-03	-6.77E-03	2.83E-03	8.57E-01			
75	-2.74E-06	1.68E-06	-2.33E-05	-5.95E-05	-4.08E-05	-8.67E-06	-1.23E-05	4.42E-05	1.22E-03		
76	1.17E-06	-1.65E-06	-9.50E-06	1.63E-05	1.02E-05	1.27E-05	-1.24E-06	-8.98E-05	-3.65E-05	2.66E-03	
77	-3.49E-05	1.83E-04	-1.94E-04	4.19E-05	-1.09E-04	7.76E-05	-1.59E-04	-2.11E-03	-3.17E-05	2.56E-05	1.63E-03
78	4.17E-06	2.26E-05	-4.59E-05	1.21E-04	1.40E-04	1.86E-05	2.96E-05	-4.42E-04	-8.54E-04	1.38E-04	1.20E-04

Parameters	78
78	2.47E-03

11.5. Appendix E: Appendix to Chapter 7

Table 49: Distribution of age among smokers across drinking and gender categories, GHS 2006 data

	Smoker, At-risk drinker		Smoker, Not at-risk drinker	
Age group	(1) Males	(2) Females	(3) Males	(4) Females
18-24	13.43%	12.95%	8.29%	9.58%
25-34	22.50%	26.11%	22.00%	18.96%
35-44	24.32%	23.78%	22.12%	21.86%
45-54	18.51%	17.83%	18.27%	19.26%
55-64	14.34%	14.01%	16.83%	16.77%
65-74	5.99%	4.03%	9.62%	9.58%
75-100	0.91%	1.27%	2.88%	3.99%
Total	100.00%	100.00%	100.00%	100.00%

The propensity to drink to at-risk levels falls with age, as shown by the higher proportion of respondents aged 55 and over in columns (3) and (4) compared with columns (1) and (2) of Table 49.

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Table 50: Published RR functions linking average daily consumption (x, grams of alcohol) to disease risk

Condition		Risk function	Source
Malignant neoplasm of lip, oral cavity and pharynx		$\ln(RR) = 0.02572x - 0.00006x^2$	Tramacere *et al* 2010 [429]
Malignant neoplasm of oesophagus		$\ln(RR) = 0.0133x$	Corrao *et al* 2004 [430]
Malignant neoplasm of colon and rectum		$\ln(RR) = -0.00000000000000002 + 0.002x$	
Malignant neoplasm of liver and intrahepatic bile ducts		$\ln(RR) = 0.00743x - 0.00001x^2$	
Malignant neoplasm of larynx		$\ln(RR) = 0.01625x - 0.00003x^2$	Islami *et al* 2010 [431]
Malignant neoplasm of breast	Female	$RR = 1 + 0.001x$	Key *et al* 2006 [432]
Epilepsy and status epilepticus		$\ln(RR) = 0.006143 + 0.012286x$	Samokhvalov *et al* 2010 [433]
Hypertensive diseases		$\ln(RR) = -0.0000000000000002 + 0.0146x$	Corrao *et al* 2004 [430]
Cardiac arrhythmias		$RR = 1 + 0.008x$	Kodama *et al* 2011 [434]
Haemorrhagic stroke		$\ln(RR) = 0.015x$	Corrao *et al* 2004 [430]
Ischaemic stroke		$\ln(RR) = -0.0432 + 0.0095x + 0.0003x^2 - 0.0000006x^3$	
Oesophageal varices		$\ln(RR) = 0.0668 + 0.0444x - 0.0001x^2$	
Gastro-oesophagel laceration	Male	$RR = 1 + 0.2779x$	Purshouse *et al* 2009 [253]
	Female	$RR = 1 + 0.4713x$	
Unspecified liver disease		$\ln(RR) = 0.0668 + 0.0444x - 0.0001x^2$	Corrao *et al* 2004 [430]
Acute and chronic pancreatitis		$\ln(RR) = 0.012x$	
Psoriasis	Male	$RR = 1.0945 + 0.014x - 0.00001x^2$	Gutjahr *et al* 2001 [435]
	Female	$RR = 1.1295 + 0.0226x - 0.00009x^2$	

Condition		Risk function	Source
Spontaneous abortion	Female	$RR = 0.953 + 0.0371x - 0.0004x^2$	
Diabetes mellitus (type II)	Male	$RR = 1.0464 - 0.0139x + 0.0001x^2$	
	Female	$RR = 1.0261 - 0.0103x + 0.0002x^2$	
Ischaemic heart disease	Male	$\ln(RR) = -0.1065\sqrt{x} + 0.01454x$	Corrao *et al* 2004 [430]
	Female	$\ln(RR) = -0.1065\sqrt{x} + 0.0207x$	
Cholelithiasis	Male	$RR = 0.9884 - 0.0075x + 0.00002x^2$	Gutjahr *et al* 2001 [435]
	Female	$RR = 0.9803 - 0.0134x + 0.00009x^2$	

Table 51: Number of patient-specific hospital admissions, by ICD-10 code, year beginning April 2005, from NWPHO report *

Condition	ICD-10	Number of patient specific hospital admissions													
		Males							Females						
		18-24	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75+**	**18-24**	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75+**
Road traffic accidents	**V(many)**	3,536	3,098	2,906	1,736	1,217	589	638	1,324	1,348	972	730	648	505	733
Pedestrian traffic accidents	**V(many)**	65.8	84	76	52	39	28	58	37.1	36	34	34	55	34	78
Water transport accidents	**V90-V94**	21.7	47	56	28	33	11	7	6.3	11	14	12	11	12	11
Air and space transport accidents	**V95-V97**	3.5	18	32	18	10	7	0	0.7	6	3	2	2	1	0
Falls	**W00-W19**	6,126	7,586	7,582	6,694	8,016	10,993	38,526	2,981	5,071	5,520	6,600	11,303	19,646	110,695
Work/machine injuries	**W24-W31**	3,249	4,289	3,708	2,247	1,549	640	280	790	1,020	939	577	337	183	160
Firearm injuries	**W32-W34**	197.4	114	78	47	27	12	5	18.9	10	15	4	5	0	1
Drowning	**W65-W74**	8.4	5	10	10	11	9	11	5.6	4	8	4	6	4	12
Inhalation of gastric contents	**W78-W79**	24.5	40	59	60	85	148	323	13.3	34	47	48	74	91	391
Fire injuries	**X00-X09**	210	240	202	140	104	92	113	56.7	83	88	64	60	60	166
Accidental excessive cold	**X31**	4.9	2	8	8	13	13	56	0	2	4	2	3	13	106
Intentional self-harm/Event of undetermined intent	**X60-X84, Y10-Y34**	3,354	4,690	4,214	2,169	1,101	532	637	6,532	5,690	5,726	3,170	1,467	759	897
Malignant neoplasm of lip, oral cavity and pharynx	**C00-C14**	22	54	208	742	1119	896	703	15	55	137	321	498	496	598
Malignant neoplasm of oesophagus	**C15**	4	20	149	651	1832	2366	2656	2	5	62	218	603	921	1925
Malignant neoplasm of colon	**C18**	20	81	279	779	2456	4206	5230	12	71	272	753	1905	3164	5430
Malignant neoplasm of rectum	**C20**	4	29	151	646	1836	2712	2531	6	40	142	386	888	1295	1895
Malignant neoplasm of liver and intrahepatic bile ducts	**C22**	10	18	51	118	298	461	549	7	13	31	85	183	296	490
Malignant neoplasm of larynx	**C32**	0	5	45	226	681	665	637	0	2	17	61	123	125	162

Condition	ICD-10	Number of patient specific hospital admissions													
		Males							Females						
		18-24	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75+**	**18-24**	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75+**
Malignant neoplasm of breast	**C50**	0	0	0	0	0	0	0	22	827	4987	8979	10229	7093	5277
Epilepsy and status epilepticus	**G40-G41**	1376	2350	3054	2974	3235	3344	4062	1763	3225	3489	3144	3220	3026	4887
Hypertensive diseases	**I10-I15**	244	492	811	1263	2312	3814	9886	166	404	554	860	1705	3290	14387
Cardiac arrhythmias	**I47-I48**	211	640	1619	3384	9159	17756	32982	247	619	981	1779	4811	12162	42213
Haemorrhagic stroke	**I60-I62, I69.0-I69.2**	81	233	508	868	1161	1467	2197	67	184	542	871	1047	1306	2952
Ischaemic stroke	**I63-I66, I69.3-I69.4**	36	164	610	1697	4444	7673	12386	43	200	506	1070	2385	5406	17418
Oesophageal varices	**I85**	34	70	176	369	455	393	275	24	49	95	176	287	329	267
Gastro-oesophageal laceration-haemorrhage syndrome	**K22.6**	216	311	261	133	177	239	353	179	172	127	91	118	153	328
Unspecified liver cirrhosis	**K73,K74**	36	106	454	583	656	503	490	39	97	243	422	734	932	867
Acute and chronic pancreatitis	**K85,K86.1**	117	425	846	970	1114	1062	1168	250	583	780	846	1074	1093	1605
Psoriasis	**L40 excl L40.5**	99	298	514	514	517	327	247	221	443	439	396	436	294	319
Spontaneous abortion	**O03**	0	0	0	0	0	0	0	6647	17174	10977	327	4	1	93
Diabetes mellitus	**E11**	54	276	988	2126	3675	5067	5207	63	323	964	1725	2580	3660	5255
Ischaemic heart disease	**I20-I25**	78	727	4754	13264	25464	29833	32581	42	265	1742	5336	10801	16068	29885
Cholelithiasis	**K80**	151	904	2266	3270	4827	6540	8243	2027	6775	9257	9118	10805	9689	13509
Alcohol-induced pseudo-Cushing's syndrome	**E24.4**	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mental and behavioural disorders due to use of alcohol	**F10**	2568	4893	7885	7440	5944	3343	1768	1162	1841	3111	2980	1958	1010	835
Degeneration of nervous system due to alcohol	**G31.2**	0	1	30	71	64	42	24	0	1	15	29	26	11	10
Alcoholic polyneuropathy	**G62.1**	0	6	9	25	33	20	11	0	4	4	15	8	5	6
Alcoholic myopathy	**G72.1**	0	0	2	8	10	5	4	0	0	1	1	1	1	1

Condition	ICD-10	Number of patient specific hospital admissions													
		Males							Females						
		18-24	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75+**	**18-24**	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75+**
Alcoholic cardiomyopathy	**I42.6**	0	7	46	119	159	103	37	0	0	6	9	11	3	9
Alcoholic gastritis	**K29.2**	46	91	128	97	55	30	14	21	19	39	28	17	9	3
Alcoholic liver disease	**K70**	13	233	1229	2316	2590	1467	522	7	167	675	1139	1091	657	267
Chronic pancreatitis (alcohol-induced)	**K86.0**	27	155	331	261	146	52	18	8	32	80	72	30	17	3
Ethanol poisoning	**T51.0**	72	112	108	55	22	6	3	113	129	153	82	25	7	3
Methanol poisoning	**T51.1**	1	3	2	4	1	0	1	2	1	4	3	0	0	2
Toxic effect of alcohol, unspecified	**T51.9**	38	53	79	36	13	3	2	56	63	76	40	20	5	1
Accidental poisoning by and exposure to alcohol	**X45**	55	55	53	34	13	9	5	54	48	54	29	13	2	7

* For eight conditions, these figures differ from those in the NWPHO report. Hostpital statistics for these conditions, mental and behavioural disorders due to use of alcohol, ethanol poisoning, epilepsy and status epilepticus, hypertensive diseases, cardiac arrhythmias, unspecified liver cirrhosis, Acute and chronic pancreatitis, diabetes mellitus, were adjusted to correct for apparent inconsistencies with HSCIC data, as described in the main text.

Table 52: Number of deaths, by ICD-10 code, year beginning January 2005, from NWPHO report

Condition	ICD-10	Number of deaths													
		Males							Females						
		18-24	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75+**	**18-24**	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75+**
Road traffic accidents	**V(many)**	384	336	301	143	113	70	102	79	58	55	40	43	48	83
Pedestrian traffic accidents	**V(many)**	38	26	30	34	33	31	89	12	5	12	16	16	19	61
Water transport accidents	**V90-V94**	2	2	3	2	6	1	1	0	0	0	0	0	0	0
Air and space transport accidents	**V95-V97**	1	1	5	7	5	2	0	0	0	1	2	1	0	0
Falls	**W00-W19**	16	38	91	108	175	241	754	4	10	29	53	82	123	1130
Work/machine injuries	**W24-W31**	1	2	7	5	5	0	2	2	0	0	0	1	1	0
Firearm injuries	**W32-W34**	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Drowning	**W65-W74**	19	16	19	21	18	12	10	0	3	1	10	8	6	6
Inhalation of gastric contents	**W78-W79**	3	6	17	15	27	25	50	0	4	5	15	7	13	81
Fire injuries	**X00-X09**	3	15	22	7	24	18	30	2	8	9	13	4	16	45
Accidental excessive cold	**X31**	2	1	4	4	5	6	12	1	0	0	1	5	3	31
Intentional self-harm/Event of undetermined intent	**X60-X84, Y10-Y34**	327	726	926	685	457	248	258	105	213	278	263	193	107	140
Malignant neoplasm of lip, oral cavity and pharynx	**C00-C14**	2	3	37	157	283	252	254	2	1	11	42	100	114	247
Malignant neoplasm of oesophagus	**C15**	2	6	57	262	875	1116	1667	0	1	15	85	246	411	1318
Malignant neoplasm of colon	**C18**	4	12	39	197	563	1216	2227	2	15	58	130	470	894	2618
Malignant neoplasm of rectum	**C20**	1	5	9	41	108	198	245	1	1	13	66	138	287	884
Malignant neoplasm of liver and intrahepatic bile ducts	**C22**	4	10	24	106	241	424	553	4	5	17	45	109	227	515
Malignant neoplasm of larynx	**C32**	0	1	5	41	109	142	183	0	0	2	15	14	30	66
Malignant neoplasm of breast	**C50**	0	0	0	5	11	23	39	2	70	552	1149	1969	1960	4595
Epilepsy and status epilepticus	**G40-G41**	41	74	113	97	65	65	98	22	55	46	48	53	39	138

Condition	ICD-10	Number of deaths													
		Males							Females						
		18-24	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75+**	**18-24**	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75+**
Hypertensive diseases	**I10-I15**	0	11	41	85	177	290	846	1	6	10	38	91	224	1642
Cardiac arrhythmias	**I47-I48**	0	2	0	6	20	91	705	0	0	0	4	13	96	1766
Haemorrhagic stroke	**I60-I62, I69.0-I69.2**	10	45	157	312	491	666	1306	10	33	144	319	473	733	2294
Ischaemic stroke	**I63-I66, I69.3-I69.4**	1	9	48	139	542	1789	8444	3	16	23	88	286	1406	16973
Oesophageal varices	**I85**	0	2	1	2	8	5	3	0	0	1	1	2	2	7
Gastro-oesophageal laceration-haemorrhage syndrome	**K22.6**	0	0	2	1	2	2	11	0	0	1	1	0	4	11
Unspecified liver cirrhosis	**K73,K74**	2	7	86	165	232	211	196	0	7	41	70	121	188	287
Acute and chronic pancreatitis	**K85,K86.1**	2	9	26	52	71	89	191	2	5	10	21	30	90	350
Psoriasis	**L40 excl L40.5**	0	0	1	1	2	2	1	0	0	0	0	1	0	3
Spontaneous abortion	**O03**	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Diabetes mellitus	**E11**	0	0	6	12	35	121	371	0	1	0	5	18	86	530
Ischaemic heart disease	**I20-I25**	8	77	704	2242	5626	10618	26342	1	17	146	477	1525	4643	29367
Cholelithiasis	**K80**	0	0	1	5	14	36	119	0	1	0	5	16	39	262
Alcohol-induced pseudo-Cushing's syndrome	**E24.4**	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mental and behavioural disorders due to use of alcohol	**F10**	5	33	71	126	105	39	19	0	10	26	47	37	10	9
Degeneration of nervous system due to alcohol	**G31.2**	0	0	0	1	0	2	1	0	0	0	1	0	1	0
Alcoholic polyneuropathy	**G62.1**	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Alcoholic myopathy	**G72.1**	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Alcoholic cardiomyopathy	**I42.6**	0	2	9	15	20	5	8	0	0	3	5	2	4	2
Alcoholic gastritis	**K29.2**	0	0	0	0	0	0	0	0	0	0	0	1	0	0

Condition	ICD-10	Number of deaths													
		Males							Females						
		18-24	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75+**	**18-24**	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75+**
Alcoholic liver disease	**K70**	2	61	382	827	802	388	139	5	41	208	427	362	167	61
Chronic pancreatitis (alcohol-induced)	**K86.0**	1	4	7	18	11	2	0	0	0	1	2	2	3	1
Ethanol poisoning	**T51.0**	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Methanol poisoning	**T51.1**	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Toxic effect of alcohol, unspecified	**T51.9**	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Accidental poisoning by and exposure to alcohol	**X45**	5	12	36	27	14	5	0	1	8	18	14	8	2	0

Table 53: English population 2005, by age and gender, ONS data [438]

Males							Females						
18-24	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75+**	**18-24**	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75+**
2352400	3362900	3866200	3177900	2879300	1983600	1477700	2260100	3374900	3906300	3232600	2971800	2206100	2383700

Table 54: Mean weekly and peak daily alcohol use among at-risk drinkers and others in England, GHS 2006 sample

	Mean weekly alcohol units				Peak daily alcohol units			
	At-risk drinkers		Not At-risk drinkers		At-risk drinkers		Not At-risk drinkers	
Age	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
18-24	45.4	30.8	6.9	4.0	13.8	9.4	3.9	2.7
25-34	44.5	30.6	7.0	3.6	13.5	8.8	4.0	2.4
35-44	42.3	29.1	7.2	3.6	10.6	8.0	4.1	2.2
45-54	46.0	31.2	7.2	3.6	10.1	6.9	3.6	2.1
55-64	47.4	28.8	6.4	2.9	9.1	5.7	2.7	1.6
65-74	42.0	23.7	5.9	2.2	6.9	4.3	2.3	1.1
75+	36.7	23.6	5.0	1.6	4.9	3.0	1.4	0.7

Table 55: Mean alcohol consumption by drinking category, gender and age, GHS 2006

		Males							Females						
		18-24	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75+**	**18-24**	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75+**
At-risk drinkers	Weekly units	45.39	44.50	42.34	45.99	47.42	42.01	36.74	30.84	30.61	29.13	31.16	28.85	23.73	23.60
	Daily units	6.48	6.36	6.05	6.57	6.77	6.00	5.25	4.41	4.37	4.16	4.45	4.12	3.39	3.37
	g/day	51.88	50.86	48.39	52.56	54.20	48.01	41.99	35.25	34.98	33.29	35.61	32.97	27.12	26.98
Others	Weekly units	6.94	6.95	7.18	7.20	6.43	5.85	5.03	3.98	3.59	3.60	3.59	2.91	2.23	1.65
	Daily units	0.99	0.99	1.03	1.03	0.92	0.84	0.72	0.57	0.51	0.51	0.51	0.42	0.32	0.24
	g/day	7.93	7.95	8.20	8.23	7.35	6.69	5.75	4.54	4.11	4.11	4.10	3.33	2.55	1.88

Table 56: Peak alcohol consumption by drinking category, gender and age, GHS 2006

		Males							Females						
		18-24	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75+**	**18-24**	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75+**
At-risk drinkers	Daily units	13.84	13.46	10.62	10.08	9.14	6.94	4.92	9.37	8.83	8.03	6.90	5.68	4.25	2.99
	g/day	110.70	107.69	84.94	80.65	73.10	55.53	39.32	74.95	70.68	64.23	55.20	45.47	34.03	23.92
Others	Daily units	3.95	4.00	4.07	3.62	2.72	2.26	1.39	2.69	2.39	2.20	2.11	1.57	1.08	0.68
	g/day	31.58	31.97	32.56	28.98	21.75	18.10	11.10	21.49	19.10	17.61	16.84	12.56	8.61	5.45

Table 57: Deaths within 90 days of admission HES-ONS linked data [540]

Primary diagnosis: 3 character code	Description	Finished admission episodes	Total deaths within 90 days
Alcohol-induced pseudo-Cushing's syndrome	**E24.4**	869	8
Mental and behavioural disorders due to use of alcohol	**F10**	47,402	721
Degeneration of nervous system due to alcohol	**G31.2**	2,331	328
Alcoholic polyneuropathy	**G62.1**	7,930	70
Alcoholic myopathy	**G72.1**	731	33
Alcoholic cardiomyopathy	**I42.6**	5,637	295
Alcoholic gastritis	**K29.2**	93,286	1,176
Alcoholic liver disease	**K70**	14,886	3,298
Chronic pancreatitis (alcohol-induced)	**K86.0**	10,884	396
Ethanol poisoning	**T51.0**	1,350	15
Methanol poisoning	**T51.1**	1,350	15
Toxic effect of alcohol, unspecified	**T51.9**	1,350	15
Accidental poisoning by and exposure to alcohol	**X45**		
Malignant neoplasm of lip, oral cavity and pharynx	**C00-C14**	19,672	1,872
Malignant neoplasm of oesophagus	**C15**	30,977	6,775
Malignant neoplasm of colon	**C18**	81,277	7,697
Malignant neoplasm of rectum	**C20**	38,572	3,080
Malignant neoplasm of liver and intrahepatic bile ducts	**C22**	8,132	2,267
Malignant neoplasm of larynx	**C32**	4,849	486
Malignant neoplasm of breast	**C50**	173,815	6,635
Epilepsy and status epilepticus	**G40-G41**	45,414	1,355
Hypertensive diseases	**I10-I15**	39,739	2,108
Cardiac arrhythmias	**I47-I48**	110,860	3,994
Haemorrhagic stroke	**I60-I62, I69.0-I69.2**	24,386	7,288
Ischaemic stroke	**I63-I66, I69.3-I69.4**	72,413	14,142
Oesophageal varices	**I85**	7,063	435
Gastro-oesophageal laceration-haemorrhage syndrome	**K22.6**	63,310	1,287
Unspecified liver cirrhosis	**K73,K74**	4,785	610
Acute and chronic pancreatitis	**K85,K86.1**	29,851	1,417
Psoriasis	**L40 not L40.5**	12,975	49
Spontaneous abortion	**O03**	44,532	6
Diabetes mellitus	**E11**	29,525	1,638
Ischaemic heart disease	**I20-I25**	287,506	15,136
Cholelithiasis	**K80**	101,040	1,199

Table 58: Distribution of age among smokers across drinking and gender categories, GHS 2006 data

	At-risk Drinkers		Not At-risk Drinkers	
Age Category	**Males**	**Females**	**Males**	**Females**
18-24 years	13.4%	13.0%	8.3%	9.6%
25-34 years	22.5%	26.1%	22.0%	19.0%
35-44 years	24.3%	23.8%	22.1%	21.9%
45-54 years	18.5%	17.8%	18.3%	19.3%
55-64 years	14.3%	14.0%	16.8%	16.8%
65-74 years	6.0%	4.0%	9.6%	9.6%
75-100 years	0.9%	1.3%	2.9%	4.0%
Total	100.0%	100.0%	100.0%	100.0%

This Table displays the distribution of GHS 2006 adult smoker respondents, sub-divided by gender and drinking status, across age categories. Smokers who are at-risk drinkers are on average younger than the remainder of the smoking sample. Over 95% of female at-risk drinking smokers are aged 18-65; this figure is just over 94% for male counterparts. By contrast, 12.5% of male smokers who don't drink above guideline levels are over 65 years old; this figure is over 13.5% for corresponding females.

Table 59: Alcohol-related costs [401, 450] and mean utility values [253, 453]

ICD-10 code	Cost of a hospital admission	Mean utility value, by age category						
		18-24	25-34	35-44	45-54	55-64	65-74	75+
E24.4	£6,453.26	0.61	0.59	0.56	0.53	0.51	0.48	0.45
F10	£6,605.56	0.57	0.55	0.52	0.50	0.48	0.45	0.42
G31.2	£18,776.16	0.61	0.59	0.56	0.53	0.51	0.48	0.45
G62.1	£11,701.47	0.61	0.59	0.56	0.53	0.51	0.48	0.45
G72.1	£14,441.75	0.65	0.63	0.60	0.57	0.54	0.52	0.48
I42.6	£9,551.50	0.65	0.63	0.60	0.57	0.54	0.52	0.48
K29.2	£13,850.34	0.54	0.52	0.50	0.48	0.45	0.43	0.40
K70	£5,142.60	0.56	0.54	0.52	0.49	0.47	0.45	0.42
K86.0	£21,481.97	0.51	0.49	0.47	0.45	0.42	0.40	0.38
T51.0	£5,143.71	0.43	0.42	0.40	0.38	0.36	0.34	0.32
T51.1	£4,973.63	0.43	0.42	0.40	0.38	0.36	0.34	0.32
T51.9	£29,880.66	0.73	0.71	0.67	0.64	0.61	0.58	0.54
X45	£2,004.35	0.64	0.62	0.59	0.56	0.53	0.51	0.47
C00-C14	£9,288.03	0.72	0.69	0.66	0.63	0.60	0.57	0.53
C15	£6,845.68	0.78	0.76	0.72	0.69	0.65	0.62	0.58
C18	£10,316.33	0.84	0.81	0.78	0.74	0.70	0.66	0.63
C20	£8,942.30	0.86	0.83	0.79	0.75	0.72	0.68	0.64
C22	£7,014.66	0.69	0.67	0.64	0.61	0.58	0.55	0.51
C32	£6,600.00	0.91	0.88	0.84	0.80	0.76	0.72	0.67
C50	£4,995.86	0.84	0.81	0.77	0.74	0.70	0.66	0.62
G40-G41	£8,715.52	0.70	0.68	0.65	0.62	0.59	0.56	0.52
I10-I15	£5,575.04	0.62	0.60	0.57	0.55	0.52	0.49	0.46
I47-I48	£7,951.80	0.77	0.74	0.71	0.68	0.64	0.61	0.57
I(many – hem strok)	£6,378.78	0.80	0.77	0.73	0.70	0.66	0.63	0.59
I(many – isch stroke)	£8,339.77	0.75	0.72	0.69	0.66	0.63	0.59	0.56
I85	£8,064.08	0.64	0.62	0.59	0.56	0.54	0.51	0.48
K22.6	£2,465.69	0.71	0.68	0.65	0.62	0.59	0.56	0.53
K73,K74	£5,108.14	0.95	0.91	0.87	0.83	0.79	0.75	0.70
K85,K86.1	£5,509.45	0.70	0.67	0.64	0.61	0.58	0.55	0.52
L40 not L40.5	£5,496.11	0.68	0.66	0.63	0.60	0.57	0.54	0.50
O03	£4,045.38	0.84	0.81	0.78	0.74	0.70	0.67	0.63
V(many - road)	£15,988.08	0.69	0.67	0.64	0.61	0.58	0.55	0.51
V(many - ped)	£25,885.31	0.73	0.71	0.68	0.64	0.61	0.58	0.54

ICD-10 code	Cost of a hospital admission	Mean utility value, by age category						
		18-24	25-34	35-44	45-54	55-64	65-74	75+
V90-V94	£6,252.05	0.93	0.90	0.86	0.82	0.78	0.74	0.69
V95-V97	£8,840.02	0.68	0.66	0.63	0.60	0.57	0.54	0.51
W00-W19	£4,730.17	0.66	0.64	0.61	0.58	0.55	0.52	0.49
W24-W31	£5,851.85	0.68	0.66	0.63	0.60	0.57	0.54	0.51
W32-W34	£5,004.75	0.68	0.66	0.63	0.60	0.57	0.54	0.51
W65-W74	£3,355.03	0.71	0.69	0.66	0.62	0.59	0.56	0.53
W78-W79	£3,905.31	0.89	0.86	0.82	0.78	0.74	0.70	0.66
X00-X09	£3,666.30	0.66	0.64	0.61	0.58	0.55	0.52	0.49
X31	£4,926.94	0.66	0.64	0.61	0.58	0.55	0.52	0.49
X60-X84,Y10-Y34	£4,693.48	0.97	0.94	0.89	0.85	0.81	0.77	0.72
X85-Y09	£5,073.68	0.66	0.64	0.61	0.58	0.55	0.52	0.49
E11	£5,866.30	0.66	0.64	0.61	0.58	0.55	0.52	0.49
I20-I25	£5,082.57	0.46	0.45	0.43	0.41	0.39	0.37	0.34
K80	£5,291.56	0.71	0.68	0.65	0.62	0.59	0.56	0.52

11.6. Appendix F: Appendix to Chapter 8

Table 60: Confounded transition probabilities to smoking next year

	Men				Women			
Behaviour last year	"NAR,NS"	"AR,S"	"AR,NS"	"NAR,S"	"NAR,NS"	"AR,S"	"AR,NS"	"NAR,S"
19-25 years old	0.076	0.842	0.165	0.816	0.044	0.826	0.090	0.829
26-35 years old	0.049	0.888	0.067	0.829	0.038	0.861	0.070	0.858
36-45 years old	0.031	0.893	0.049	0.875	0.028	0.890	0.043	0.867
46-55 years old	0.023	0.876	0.046	0.893	0.021	0.865	0.038	0.878
56-65 years old	0.014	0.926	0.026	0.868	0.015	0.880	0.028	0.840
66-75 years old	0.010	0.826	0.018	0.883	0.010	0.840	0.007	0.846
76-101 years old	0.007	0.714	0.015	0.832	0.004	0.889	0.017	0.909

Table 61: Confounded transition probabilities to at-risk drinking next year

	Men				Women			
Behaviour last year	"NAR,NS"	"AR,S"	"AR,NS"	"NAR,S"	"NAR,NS"	"AR,S"	"AR,NS"	"NAR,S"
19-25 years old	0.095	0.590	0.552	0.195	0.068	0.566	0.533	0.187
26-35 years old	0.056	0.659	0.651	0.133	0.041	0.657	0.596	0.090
36-45 years old	0.054	0.816	0.749	0.113	0.036	0.780	0.676	0.077
46-55 years old	0.064	0.793	0.774	0.085	0.041	0.821	0.680	0.056
56-65 years old	0.053	0.828	0.797	0.085	0.030	0.779	0.732	0.054
66-75 years old	0.051	0.856	0.795	0.078	0.020	0.731	0.705	0.049
76-101 years old	0.034	0.861	0.799	0.010	0.015	0.667	0.508	0.033