The development of the Economic impacts of Smoking In Pregnancy (ESIP) model for measuring the impacts of smoking and smoking cessation during pregnancy

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Abstract

1.1 Background

Smoking in pregnancy is a major cause of morbidity and mortality [1-3], with a significant cost burden to the NHS. [4] An estimated 26% of women still report smoking at the beginning of or just before pregnancy, with 12% reporting smoking throughout. [5]While economic evaluations of cessation interventions in the non-pregnant population are well developed, similar evaluations of within-pregnancy interventions are not. [6] Because of the special circumstances associated with pregnancy, general smoking evaluations cannot be applied in these settings. [4, 5] This thesis outlines the development of an improved economic model designed to capture the healthcare costs and benefits associated with smoking and cessation within pregnancy.

1.2 Methods

A series of scoping reviews of the electronic resource Medline were conducted to identify either within-pregnancy or childhood morbidities which had potentially causal associations with smoking during or after pregnancy, as well as the incidences of morbidities and health related quality of life (HRQoL) scores attributable to those identified. A systematic review appraised the previous economic literature on cessation during pregnancy, to determine where improvements were needed. To ensure that relapse to smoking could be accounted for, a second systematic review generated pooled estimates of abstinence from smoking in the postpartum period. This information was used to develop and construct the improved economic model.

1.3 **Results**

11 conditions were identified as having a causal association with smoking during pregnancy. The systematic review of previous evaluations identified 17 studies; however, only three were considered high quality, suggesting the need for an improved model. The pooled estimates of abstinence suggested that by two years postpartum, most women had restarted smoking, with most relapsing after three, but before 12, months postpartum. The Economic impacts of Smoking In Pregnancy (ESIP) model consists of two linked decision trees which capture the within-pregnancy aspects, while two linked Markov chains capture the post-pregnancy smoking behaviour for both the mother and her child. ESIP was also extended to control for uncertainty.

1.4 **Conclusion**

ESIP improves on the previous literature since it directly captures the impact of the mother's smoking behaviour on the health of her offspring, both within-pregnancy and childhood, using the most accurate data currently available. Future extensions to ESIP include an adult component for the infant to capture their smoking behaviour.

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List of contributors

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Appendices: All appendices were generated by MJ except for Appendix 12.8 where MS was the lead author.

List of abbreviations

ACER	Average cost-effectiveness ratio
AHCPR	Agency for Health Care Policy and Research
AUD	Australian dollars
BMJ	British Medical Journal
CBA	Cost benefit analysis
CBT	Cognitive behaviour therapy
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curves
CHD	Coronary heart disease
CHEC	Consensus health economic criteria
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence interval
CM	Cost minimisation
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disorder
CPS II	American Cancer Society's Cancer Prevention Study
CUA	Cost utility analysis
DALY	Disability adjusted life year
DAM	Decision Analytical Model
DoH	Department of Health
ESIP	Economic impacts of Smoking In Pregnancy
EVPPI	Expected value of perfect parameter information
FL	Foetal Loss
HES	Hospital Episode Statistics
HMO	Health Maintenance Organisation
HRG	Healthcare Resource Groups
HRQoL	Health related quality of life
ICC	Infant Childhood Component
ICER	Incremental cost-effectiveness ratio
IFS	Infant Feeding Survey
INB	Incremental net benefit
IWPC	Infant Within-Pregnancy Component
LBW	Low birth weight

LC	Lung cancer
LY	Life year
LYG	Life years gained
LYS	Life years saved
MI	Myocardial infarction
MLC	Mother's Lifetime Component
MVI	Motivational interviewing
MWPC	Maternal Within-Pregnancy Component
NBW	Normal birth weight
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NMB	Net monetary benefit
NICE	National Institute for Health and Care Excellence
NICU	Neonatal intensive care unit
NRT	Nicotine replacement therapy
OAC	Offspring Adult Component
ONS	Office for National Statistics
OR	Odds ratio
PA	Physical activity
PP	Postpartum
p.p.m.	Parts per million
PPROM	Preterm premature rupture of membranes
PR	Post randomisation
PROM	Premature rupture of membranes
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
QHES	Quality of Health Economic studies
RCP	Royal College of Physicians
RCT	Randomised controlled trial
RR	Relative risk
s.d.	Standard deviation
SAMMEC	Smoking-Attributable Morbidity, Mortality, and Economic Costs
SIDS	Sudden infant death syndrome

SoC	Stages of change
UC	Usual care
UK	United Kingdom
US	United States
USD	United States Dollars
VOI	Value of information

Chapter 1: Introduction.

1.1 Smoking in non-pregnant populations

Smoking is a major and preventable cause of morbidity and mortality, killing an estimated six million people globally each year. [7] Smoking was attributable to an estimated 81,700 deaths in 2010 in the United Kingdom (UK), around 35% of all deaths of adults aged 35 years or older. [8] Smoking has been linked with lung cancer, respiratory diseases, cardiovascular disease, and other serious health conditions, all of which are important causes of mortality. [9] Around 22,300 (36%) of all respiratory disease related deaths and 37,500 (29%) of all cancer deaths among adults aged 25 or over were attributable to smoking in 2010. [8] Smoking not only has direct effects on the smoker, but can lead to increased mortality in the non-smoking population. Passive smoking at home in the UK potentially accounts for 2,700 deaths per year in persons aged between 20 and 64 years and 617 deaths a year from workplace passive smoking. [10] Despite high profile public health campaigns, the prevalence of smoking in the UK has remained relatively static in recent years, with 21% of the UK population reporting smoking in 2009, the same as in 2007 and 2008. [8] Internationally, this is slightly more than the 19.3% in the United States (US) [11] and 16.4% in Australia [12], but slightly less than in other countries in Europe such as France (27%) and Germany (25%) [7]. In the UK, smoking tends to be more prevalent in men than in women, with 22% and 20% smoking respectively. [8]. Smoking is cited as one of the principal causes of health inequality between rich and poor. [13] In the UK in 2009, the prevalence was lowest in the highest income quartile households (14% for men, 11% for women), and highest in the lowest quintile households (40% for men and 34% for women). [8]

1.2 UK economic burden of smoking outside of-pregnancy

The prevalence of smoking puts a large economic burden on the National Health Service (NHS). In 2009/10 approximately 5% (461,700) of all people admitted to hospital aged over 34 years were attributable to smoking [8], and in 2005/6 smoking was estimated to cost

the NHS £5 billion, or 5.5% of that year's total NHS expenditure. [14] However, it has been suggested that this is an underestimation and the true value could be around 15% of total healthcare costs. [15] It is also estimated to cost a further £12.8 million (at 2002 prices) through the effects of passive smoking in non-smoking adults. [15] With such a large economic and disease burden, it is understandable why smoking remains such an important public health issue.

1.3 Smoking during pregnancy

Smoking during pregnancy has severe health consequences for both the mother and infant. Not only is the mother increasing her risks of developing smoking-related diseases (e.g. lung cancer), but she is exposing herself to greater risks of pregnancy-related conditions that can severely jeopardise her health and that of her infant, potentially proving fatal for either, or both. Strong evidence has demonstrated that smoking during pregnancy can lead to increased risks of the following conditions [2]:

- ectopic pregnancy: where the foetus develops outside the uterus; potentially fatal for the mother, always fatal for the foetus
- placenta previa: where the placenta covers the cervix and can lead to vaginal bleeding
- placental abruption: the placental lining separates from the wall of the uterus, leading to vaginal bleeding, common contributor to maternal mortality
- preterm premature rupture of the membranes (PPROM): rupture of the membranes before 37 weeks gestation, leading to labour

Smoking during pregnancy is also the potential cause of up to 4,000 deaths per year from miscarriage and stillbirth. [16] Furthermore, there is strong evidence that it is a determinant in increasing the risks of premature birth (infants born before 37 weeks gestation) and low birth weight (LBW) (infants born weighing less than 2500 grams), which often require support in paediatric intensive care units. [17] There is growing evidence that links smoking during pregnancy with longer term health issues for the infant. Chronic conditions such as asthma and other respiratory illnesses have been widely established as

being associated with smoking during pregnancy. [1, 4] These can severely impact on the child's life, reducing their quality of life and potentially hampering their integration into society. [18]

Despite evidence of the adverse effects of smoking, smoking during pregnancy remains a significant international problem. In the UK, in 2010, 12% of mothers smoked throughout their pregnancy and 26% smoked either during or in the 12 months before pregnancy. [5] In Spain, the rate is reported to be as high as 39.4% [19], while in other countries such as Australia, the US, and Germany rates are 14.5%, 14.1%, and 13% respectively. [20-22] Other countries report lower rates; for example, Canada's prevalence is 10.5% [23], but this is still a substantial proportion of the population. However, pregnancy provides an incentive for mothers to quit, and in the UK, 54% of smokers stop smoking before child birth. [5] Mothers in routine and manual work occupations report higher smoking prevalence than those in professional and managerial occupations (40% versus 14% respectively). [5] Those classified in the more deprived socio-economic groups also report the lowest quit rate, with 50% reporting quitting by birth, compared with 72% in the highest socio-economic group. [5]

Unfortunately, the Infant Feeding Survey (IFS) does not report rates of relapse to smoking after birth, although this has been estimated to be quite high, at between 67% and 80% during the first year after pregnancy. [4] Not only does this have direct health consequences for the mother, but it also exposes the infant to the risks of passive smoking, such as doubling the risk of sudden infant death syndrome (SIDS) and increasing the risks of wheezing and other respiratory problems by 20% to 40%. [24] More recently, evidence has demonstrated that if the mother smokes, the infant is over twice as likely to become an adult smoker [25], exposing their life to the excess health effects of smoking and potentially producing a cycle that could carry on for generations.

The economic burden of smoking during pregnancy is substantial, costing the NHS up to £64 million annually. [4] A substantial proportion is attributable to infant outcomes, with conservative estimated costs of £23.5 million for the first year of life. [4] It is possible that by including the potential effects of passive smoking and chronic diseases such as asthma

on the child, the cost could be substantially greater. In the US, it is estimated that smoking during pregnancy increases neonatal costs by over USD 700 per child (£416.08[1]), and is attributable for almost USD 367 million (1996 prices) (£218,144,800[2])in neonatal costs for the US as a whole. [26] Since smoking during pregnancy is preventable, it is understandable why this topic remains a serious public health concern.

1.4 Effectiveness of cessation interventions during pregnancy

Systematic reviews have investigated smoking cessation interventions in pregnancy. Coleman et al conducted a meta-analysis of six trials of 1,745 women to investigate the effectiveness of nicotine replacement therapy (NRT). [27] The review looked at four trials where the control group were placebo randomised control trials (RCTs) and two studies which involved an intervention arm with both NRT and behavioural support, with the control group only receiving behavioural support. Combining all studies, the pooled relative risk (RR) for NRT was 1.33 (95% confidence interval (CI) 0.93 to 1.91). In the sensitivity analysis, when using only biochemically validated data, the RR was 1.40 (95% CI 0.97 to 2.04). For placebo controlled trials, there was no evidence of a benefit in quitting with NRT, whereas in non-placebo trials there was a significant effect estimate with an RR of 7.81 (95% CI 1.51 to 40.35). The authors concluded that there was insufficient evidence to demonstrate that NRT used by pregnant women for smoking cessation was effective or safe. Since no other pharmacological interventions are licensed to be used within pregnancy, this suggests that these interventions would appear ineffective, but this may be due to the lack of currently available data.

A recent Cochrane review investigated psychosocial interventions designed to support women stopping smoking in pregnancy. [28] The review identified six types of intervention:

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[1] Converted August 2nd 2014 USD1 = 0.5944
http://www.dollars2pounds.com/ExchangeRate/USD/GBP

[2] Converted August 2nd 2014 USD1 = 0.5944
http://www.dollars2pounds.com/ExchangeRate/USD/GBP

1. Counselling; includes motivational interviewing (MVI), cognitive behaviour therapy (CBT), providing motivation to quit and improved problem-solving and coping skills. Interventions may be delivered face-to-face, by telephone or by computer programmes. Counselling may be provided by a range of personnel, both healthcare professionals and others, and duration varied between less than five minutes to up to an hour per session.
2. Health education; includes providing women with information about the risks of smoking and advice to quit; no further support given. Usually delivered by self-help manuals or automated text messaging.
3. Feedback; informing the mother of the foetal health status or measuring the by-products of smoking to encourage the mother to quit.
4. Incentives; a financial or other form of reward contingent on smoking cessation
5. Social support; either peer or partner
6. Other; includes exercise and intensive dissemination interventions.

The review included 77 RCTs with a total of over 24,000 women included in the meta-analysis. At the primary outcome of late pregnancy, the most effective intervention appeared to be feedback, with an RR of 4.39 (95% CI 1.89 to 10.21), based on seven trials. Incentives were second, with an RR of 3.59 (95% CI 0.10 to 130.49), however this was only based on four trials and the authors suggested interpreting this with caution. When comparing counselling with usual care, the RR was 1.44 (95% CI 1.19 to 1.75) suggesting a significant effect. However, for health education and social support versus usual care there seemed to be no significant effect on quit rates with RRs of 1.51 (95% CI 0.64 to 3.59) and 1.29 (95% CI 0.94 to 1.78) respectively.

The authors concluded that psychosocial interventions were effective at supporting women in stopping smoking during pregnancy. However, all the interventions appeared to have varying degrees of effectiveness and certain interventions seemed better in some situations than others. These should be considered when delivering an intervention to smoking women. The review also highlighted that using these interventions appeared to give a significant reduction in both premature births (18%) and in the proportion of babies born with LBW (18%). Therefore it would appear that from a population level, these interventions could be seen as particularly effective.

1.5 Why economic evaluation is important

Regardless of the country or the healthcare system used, demand for healthcare usually exceeds supply, and hence the amount of care given can be equalised either by the use of monetary criteria or by some definition of need. [29] This means healthcare has to be rationed, which occurs when an individual is deprived of care which is of benefit to them, and this takes place both in private healthcare systems, where the care delivered is a result of insurance cover, and in a state-funded healthcare system where non-price rationing determines access.[29] In a country like the UK, the state-funded healthcare system has a fixed budget; for example, for 2013/14 the NHS England budget was £95.6 billion to deliver healthcare within England. [30] The population of England in mid-2013 was 53.9 million, all of whom in theory could demand some form of healthcare, which is theoretically feasible if the healthcare cost associated with each individual is less than £1,773.66. [31] This budget has to cover all healthcare, including the overheads for running the NHS, staffing, current available treatments, as well as covering the expenditure of any new technologies introduced. Maynard stated that there were six fundamental assumptions associated with rationing healthcare: the role of health care is to improve health and reduce inequalities in health; access to care is determined based on need and not ability to pay; need can be either a demand (patients want care) or supply (doctors supply care to meet a need) concept; how the need principle achieves efficiency within equity goals; the role of judging needs of competing patients should be given to independent and neutral experts; and that doctors have their performance managed and monitored to ensure they do not undermine this process. [29] Maynard concluded that if one or more of these assumptions were to be ignored, then resource allocation would be wasteful, and allocative efficiency (the optimal allocation of goods and services, where marginal benefit to consumers equals marginal cost of producing [32]) would not be achieved. [29]

When introducing a new health technology, it has to compete with existing healthcare processes; however because we practise non-price rationing, it is necessary to determine whether the new technology is an appropriate use of resources. [33] As part of this decision process, the policy maker needs to be able to determine whether the new

technology offers value for money; is the increased healthcare cost warranted by the increased benefits. It is important to demonstrate this, as the introduction of an intervention which is wasteful of resources could lead to a reallocation of NHS resources which could make society worse off. For example, Claxton et al suggested that had the drug ranibizumab been introduced in 2011, it is estimated that it would have cost the NHS an extra £80 million per annum to treat the eligible population, but resulted in 411 additional deaths because of the reallocation of resources.[34] One approach to determine value for money is to use economic evaluation, which has been defined as the comparative analysis of alternative courses of action in terms of both their costs and consequences. [33] Economic evaluation demonstrates to the policy maker whether the intervention offers value for money, or whether it is cost-effective, allowing a policy maker to decide whether a new intervention/drug should be made available by the state funded healthcare service. In the UK, since 2004, cost-effectiveness has been an important criterion in decisions about use of healthcare interventions in the NHS. [35] It is also an integral part of the (National Institute of Health and Care Excellence) NICE reference case, which is the gold standard for the decision-making process in the UK. [36] Furthermore, economic evaluation is used widely across the globe, informing the decision process in Australia, Canada, and many others.[37, 38]

1.6 Process of economic evaluation

1.6.1 Initial considerations for economic evaluations

When first developing an economic evaluation, the initial stage is the setting of the research question the evaluation is aiming to answer. [33, 39] A simple example would be that a different evaluation would be required to answer a question of technical efficiency (*how* to deliver a new service/intervention) compared to a question of allocative efficiency (*should* we use the new service/intervention); the required outcomes and costs to be collected are likely to be very different (e.g. intervention effectiveness for allocative efficiency versus intervention reach for technical efficiency). The research question may be specified by the policy/decision maker; either way the question should be clear and may

state some explicit requirements for the evaluation (e.g. a particular population or healthcare setting).

The second consideration for designing evaluations, which is closely linked with the research question, is the setting for the evaluation: either within-trial, or as a separate hypothetical decision analytical modelling exercise. A within-trial analysis is an economic evaluation which is conducted alongside a clinical trial, usually with the trial directly collecting data required to inform the effectiveness and costs associated with the new intervention and its comparator. [40] Decision analytical modelling (DAM) is an alternative to within-trial analysis when either conducting a clinical trial is impractical or multiple interventions require evaluating, which would not be possible in a single trial. [39, 41] DAM compares expected outcomes and costs of new interventions or decision options by synthesising multiple sources of data (e.g. literature based estimates, national statistics, expert opinion) using mathematical techniques to produce estimates. This provides decision makers with the best available evidence on which they can base their decision. This chapter and thesis will primarily focus on methods associated with DAM and not within-trial analyses, although some methods associated with within-trial analyses will be alluded to where relevant. This is because this thesis is not being conducted alongside a clinical trial and will be utilising DAM methods. For a more detailed summary on economic evaluation alongside within-trial analyses, see Petrou et al and Glick et al. [40, 42]

1.6.2 Perspective of analysis and time horizon

Once the research question has been specified, the next critical consideration is the perspective and time horizon to be utilised in the evaluation. [33, 39] Time horizon refers to the length of follow-up to be included in the evaluation. This could be relatively short, for example one year if part of within-trial analysis, or could be considerably longer, such as 40 or 50 years if modelling the remaining life expectancy of a patient as part of a DAM. [39] Although the time horizon can be specified by the research team, it should reflect not only the requirements of and conditions/impacts of interest to the decision maker, but also capture all the differences in costs and outcomes that are associated with both the intervention and its comparator. [36, 43]

The study perspective refers to the viewpoint from which the intervention and comparator's costs and outcomes are being considered and evaluated. [33, 43] An evaluation conducted with a narrow perspective, for example institutional (e.g. hospital), may only include costs and associated outcomes directly related to the intervention and the hospital, such as the cost of the intervention and the number of bed days saved within the hospital. A broader perspective, for example societal, would not only include these direct healthcare costs, but may also include productivity loss due to sickness, family out-of-pocket expenses, and costs to the criminal justice system. Like the time horizon, the perspective may be set by the research team; however, it is common for the decision maker to pre-specify the perspective of the analysis. For example, in the UK, NICE specifies that all evaluations include a NHS and Personal Social Services perspective [36], which covers all direct health benefits associated with the patient, all direct costs to the NHS, and indirect health care costs from community-based care, but not productivity costs associated with the patient. Other countries, such as Austria and Australia, adopt the broader societal perspective [37, 44], while in the US it is common to adopt the narrower payer/insurer perspective which only covers the direct healthcare costs and benefits. [45]

1.6.3 Types of analysis

There are several types of economic analysis used in healthcare evaluations; however all consider costs in monetary units. The difference occurs in how the effectiveness of new interventions is evaluated. All types of analysis are ways of estimating which interventions/services offer value for money to the decision maker. What follows is a brief summary of the most common types of analysis;

1.6.3.1 Cost-minimisation (CMA)

In CMA, all interventions are assumed to have equal effectiveness, and hence interventions can be ranked cheapest to most expensive, with the cheapest option being chosen as the intervention of choice. [33] One of the advantages of CMAs is that they are inherently easy

to conduct and interpret, and are particularly useful where the treatments have been demonstrated to have clinical equivalence. [46] For example, CMAs are often used for non-inferiority trials, where the intervention is demonstrated to be not clinically worse than its comparator to a specified end-point. [46, 47] However, it is often found that interventions are not equivalent, for example either in effectiveness or safety, which means that CMA cannot be utilised. [48] An example where CMA may lead to a wrong decision is the Scottish Unexplained Infertility Trial. [49, 50] This trial found that intrauterine insemination was significantly more expensive than expectant management, but did lead to an insignificant increase in additional live births; therefore the CMA concluded that expectant management was the treatment of choice. However, using CEA, Dakin et al suggested that the incremental cost per additional live birth was £5,604, and concluded that intrauterine insemination was ultimately cost-effective. [51]Furthermore, Dakin et al demonstrated that CMA was still being used and that it was biasing the measurement of uncertainty and the estimates of the probability of the treatment being cost-effective, suggesting that incorrect decisions were being made on the basis of evaluations producing incorrect results. [51] This could lead to society not gaining allocative efficiency in that it is losing resources by investing in inefficient interventions.

1.6.3.2 Cost-effectiveness (CEA)

In CEA, costs are compared to the effectiveness of the intervention as measured in a natural scale, e.g. years of life gained, number of cases detected, number of disease-free days. [33] The output for a CEA can be seen as a directly relevant statement of the value for money of the new intervention, which could be considered clinically relevant to both clinicians and patients. [52] However, CEA makes it difficult to compare the value for money of multiple interventions for different diseases across a healthcare service since they may use different outcomes, making comparison between the evaluations inappropriate. [33]

1.6.3.3 Cost-utility (CUA)

CUA is a sub-group of CEA, utilising the same approach, except the outcome is measured as a generic measure of health related quality of life, taking into account patients' preferences (utility). [33] Common outcomes used (which will be described in more detail later in this chapter) are Quality Adjusted Life Years (QALYs) and Disability Adjusted Life Years (DALYs), which are generic and represent a patients' preference of being in a certain health state (e.g. limited mobility, bedridden, persistent vegetative state) for a given period of time (e.g. one year). Because of the generic nature of the outcome utilised in a CUA, this allows comparison of multiple interventions for different diseases across a healthcare service due to the use of this single, "utility" based measure. [53] Because of this comparability across all disease categories and the healthcare system, CUA rather than CEA tends to be favoured by governing bodies such as NICE. [36] However, CUA can be limited in that utility can be sufficiently insensitive to changes in milder conditions which may be important to the patient, and that the utility that society attaches to health are not unrelated to the characteristics of the individual experiencing the health, with health gains associated with severe health states potentially more highly valued than those in milder health states. [54] Furthermore, there is evidence that QALYs are unreliable, since the method used to elicit the patient's preference rate can highly influence the reported weight. [55]

1.6.3.4 Cost-benefit (CBA)

CBA is a broader approach than CEA and CUA, with the effectiveness and outcomes of the intervention valued in monetary units. [33] Because CBA values everything in money, this allows the inclusion of wider concerns associated with the intervention, such as investments in other sectors of the economy other than healthcare. [56] Early approaches to cost-benefit analyses involved the use of Grossman's Human Capital Approach (HCA) [57], whereby it was assumed that human beings could be treated as capital equipment, and that their future productivity can be assumed to be equal to their future rate of pay, and hence any gains from healthcare can be measured as the future flow of income that would have otherwise been forgone if the person had been sick. From an economist's

perspective, when a decision maker is making a decision regarding healthcare, they are implicitly applying a value on a human life, therefore using the HCA within CBA is explicitly stating this value. [56] However, the use of the HCA has been described as "unethical" because it is putting a price on a life, and that people who are unemployed (e.g. retired individuals) appear to have no benefits from healthcare as calculated by the HCA. [56] An alternative to the human capital approach is the "willingness to pay" approach (WTP), whereby an individual is directly asked how much they are willing to pay to improve their quality of life or reduce their risk of death. [58] The advantage of the WTP approach is that in theory it directly represents an individual's preference for a particular health state, taking into consideration all other concerns of the individual [56], yet there is evidence that individuals adjust their responses to take into account ability to pay, hence not revealing their true preference. [59] Additionally, it has also been suggested that WTP is insensitive to the magnitude of health benefit, with individuals reporting similar values for both interventions that give small benefits compared to those which generate large benefits, hence over-inflating the benefits associated with the small interventions. [60] Another common criticism of CBA is that because of its broad scope, necessitating both health and non-health benefits, it requires all costs and benefits associated with the intervention, which may not be possible as it needs levels of data that are not available, or beyond the capabilities of researchers to estimate. [33] For example, Schoenbaum et al evaluated a rubella vaccination using a CBA with an HCA approach. [61] The analysis included consequences not only associated with medical cost savings, but also the productivity gains from reduced disability and premature death. However, the analysis failed to take into account the additional gains to be had from the positive externality from people being unable to catch rubella from one another because they were vaccinated, which would have further increased the benefits associated with vaccination, suggesting that the estimates generated by Schoenbaum et al were conservative. However, calculating the productivity gains from the externality would have been intensely complicated, and it may not be possible to assign an accurate value to capture these gains.

1.6.3.5 Cost-consequence (CCA)

A CCA is where the outcomes of an intervention are reported separately to the costs associated. [62] It has been suggested that the common outcomes generated by the other

evaluation approaches are not particularly useful for decision makers, and that presenting disconnected outcomes (e.g. life years gained, QALYs gained, number of premature deaths averted) in a tabulated form alongside estimated costs is more useful for the decision maker, and more transparent. [62] Conversely, it has been argued that CCA can complicate the decision making process, since the decision maker may not be able to determine what is a meaningful increase in outcome for the patient, and that it reduces the comparability across the healthcare sector. [33, 63]

1.6.3.6 Cost-offset (COA)

COA involves the comparison of the intervention cost with the healthcare savings it generates, i.e. does the intervention generate medical cost-savings which can outweigh the benefits? [64] COA is a form of limited CBA, since COA does not take into account any benefits of treatment to the patients, focusing purely on the medical cost-savings generated by the treatment; however the outcome is expressed in monetary values. [64]

1.6.3.7 Which method?

The choice of method is purely down to the perspective of the analysis and requirements of the decision maker. Since the ultimate aim of this thesis is to develop an economic model which will inform the UK governing body, NICE, the thesis will focus on the use of CEA and CUA rather than the other methods. This is because NICE require the use of CUA and CEA as part of their reference case. [36]

1.6.4 Measuring effectiveness

This section discusses the sort of outcomes that may be relevant to smoking in pregnancy, which could be used as the measure of effectiveness in an economic evaluation with a particular focus on those in a CEA and CUA.

1.6.4.1 Measures for effectiveness in CEA

As has already been defined, the effectiveness of an intervention is measured in a natural scale under a CEA. There are several possible outcomes which could be utilised to measure the effectiveness of cessation during pregnancy. For the mother, smoking has been linked to several within-pregnancy conditions, such as placenta abruption, placenta previa, and ectopic pregnancy. [2] The comparison with costs could be made using number of placenta abruptions avoided, number of ectopic pregnancies prevented, or, if wishing to combine all the within-pregnancy conditions, number of adverse pregnancy outcomes avoided. These would be seen as relevant to the decision maker, clinician, and patient should the decision-making process be interested in a within-pregnancy time horizon. Conversely, although previous evaluations of cessation within-pregnancy have included these complications, they have not been used as the measure of effectiveness in the evaluation. [65] However, if a longer term time horizon is required, then a likely measure of effectiveness is life years gained (LYG), which is the difference between the intervention and usual care groups measured in terms of the number of individuals who are still alive at later time points or at the end of the simulation. LYG take into account the premature mortality of disease/health-risk behaviour. Other possible alternatives for the mother could be to use number of Coronary Heart Disease (CHD) events avoided, or number of Chronic Obstructive Pulmonary Disorder (COPD) events avoided, as smoking has been linked to increased risk of CHD and COPD. [66] However, it should be noted that although these outcomes for the mother appear relevant, if a comparison was to be made between either other cessation or other healthcare interventions, the CEAs would not be comparable unless the measures of effectiveness were the same (e.g. LYG).

For the infant, there are within-pregnancy conditions which could be used as the measure of effectiveness within an evaluation. Smoking during pregnancy has been associated with low birth weight (LBW), premature birth, and miscarriage. [3, 67] Suitable measures could be: number of LBW infants prevented, number of premature births prevented, number of infants lost avoided, and the all-encompassing number of adverse pregnancy outcomes for the infant avoided. Previous evaluations of cessation within-pregnancy have utilised similar measures of effectiveness, including LBW avoided [68, 69], so there is a precedent for using these outcomes. When considering post-pregnancy for the infant, LYG could be used, but

smoking within-pregnancy has been linked with childhood asthma [70], so a possible alternative could be number of childhood asthma cases prevented. Some previous evaluations have focused on the use of SIDS averted [71], but this is an only short-term outcome, limited to one year post pregnancy.

1.6.4.2 Measures of effectiveness in CUA

There are two common measures used for measuring effectiveness in CUA: Quality Adjusted Life Years (QALYs), and Disability Adjusted Life Years (DALYs). A QALY is a measure of a length of time spent in a particular health state weighted by its quality of life; hence it represents the burden of disease. [72] A QALY is calculated by weighting a life year by a preference value which represents the patient's preference/utility of being in that health state [73], where utility refers to the economic definition of satisfaction experienced from consuming a particular good. [32] The preference weighting has a value ≤1, where one represents perfect health and zero represents death; however, negative values can exist if patients perceive a health state to be worse than death. Furthermore, Weinstein et al summarised the underlying assumptions of the conventional QALY approach as [74]:

- Resources are limited and each intervention/alternative has resource implication
- A resource-allocation must be made, hence we are rationing healthcare
- The decision maker is interested in maximising the health stock of the population subject to resource constraints
- Health is expressed as preference (desirability)-weighted time across the relevant time horizon
- Individuals are risk-neutral (neither averse to risk or seeking risk) with respect to longevity
- Preference scores can be additive across time and can be aggregated for the group
- QALYs can be aggregated across individuals (i.e. a QALY is a QALY regardless who gains it)

There are several methods of determining preference rates, however the most common method, as recommended by NICE in the UK, is use to the generic health related quality of life questionnaire, EuroQols EQ-5D. [36, 75] The advantages of the QALY approach is that it provides a common currency to assess the extent of the benefits gained from healthcare

interventions, and that it reflects the value judgement that just survival is an insufficient measure of health benefit. [76] However, the QALY approach is not without its limitations. One assumption is that a QALY is a QALY, i.e. that a QALY gained/lost is blind to health conditions and personal characteristics; however, if society is interested in targeting specific population groups, e.g. the socioeconomically disadvantaged, this would suggest that a QALY for one group of people is not the same as for another group. [77] Furthermore, it has been argued that the QALY does not capture all the benefits generated by a healthcare intervention, particularly if the generic instruments are utilised on conditions which only lead to small changes in the health of the individual. [77] A particular example of this is the EQ-5D's apparent inability to pick up changes in hearing when persons with hearing complaints receive hearing aids. [78]

An alternative to the QALY is the DALY, which can be considered as one lost year of healthy life. [79] The formula for calculating a DALY is, as defined by the World Health Organisation (WHO) [79]:

$$DALY = Years\ of\ Life\ Lost\ (YLL) + Years\ lost\ due\ to\ Disability\ (YLD) \quad \textbf{(1.1)}$$

Where:

$$YLL = Number\ of\ deaths \times standard\ life\ expectancy\ at\ age\ of\ death\ in\ years \quad \textbf{(1.2)}$$

And:

$$YLD = Number\ of\ incidencent\ cases \times disability\ weight \times average\ duration\ of\ the\ case\ until\ remission\ or\ death\ (years) \quad \textbf{(1.3)}$$

Or:

$$YLD = number\ of\ prevalent\ cases \times disability\ weight \quad \textbf{(1.4)}$$

The YLL corresponds to the number of years lost due to premature mortality associated with the disease, while the YLD represents the years of healthy life lost due to people having to suffer the consequences of the condition. By summing the DALYs across the population, the disease burden can be calculated. In comparison to the QALY, while the QALY represents the preferences of individual health states, the DALY reflects the degree to which health is reduced by a disease condition. However, unlike the QALY, the DALY

applies an age-weighting function which values differently depending on the age of disease onset, giving a greater weight to a year lived as young adult compared to a child or elderly person. [73] DALYs are recommended for use in CEAs used to inform the World Health Organisation (WHO). [80] However, the DALY has been criticised for including this age-weighting function when there is no evidence that supports the assumption, that DALYs do not cover multiple causes, and that the minimisation of DALYs as the criterion for decision making could lead to perverse outcomes such as allocating fewer resources to a disabled person than an able-bodied person. [81, 82]

For this thesis, the measure of effectiveness will be QALYs and not DALYs, as recommended by NICE guidance. [36]

1.6.5 Measuring costs

As important as measuring the effectiveness of any intervention is the measurement of costs associated with it. However, unlike measuring effectiveness, costs are measured in the same way across all types of evaluations, in monetary units. The costs included within the evaluation are determined by the perspective of the analysis, with broader perspectives requiring more cost data. [33] For example, from a provider's perspective, patients' travel costs would not be seen as important, but these are considered important from a patient's viewpoint and a society viewpoint. The allocation of costs can be split into three categories:

- Direct costs: costs immediately associated with the intervention, for example consumables, staff time, medical supplies
- Indirect costs: costs to society incurred as a result of participating in the intervention/disease, for example patient's work loss due to ill health/treatment, reduced social and leisure activities
- Intangible costs: cost of anxieties or cost of quality of life that result from the intervention

While it is common for economic evaluations to include both direct and indirect costs, intangible costs are very difficult to measure and value, and hence are generally omitted.

[83] However, there is a distinction between the types of cost used in an evaluation. Drummond et al defined the different types of cost as [33]:

- Total cost (TC): all costs associated with the production of a output of health (q), defined as

$$TC(q) = FC + VC(q) \quad \textbf{(1.5)}$$

- Fixed cost (FC): costs which are not dependent on output in the short term (usually one year), e.g. building, equipment, rent, but may vary with time
- Variable cost (VC): costs that vary with the level of output of health, such as supplies, food, personnel, defined as a function of output $VC(q)$
- Average cost (AC): cost per unit produced, defined as

$$AC(q) = TC(q) \div q \quad \textbf{(1.6)}$$

- Marginal cost (MC): the extra cost of producing one extra unit of output, defined as

$$MC(q) = \Delta TC(q) \div \Delta q \quad \textbf{(1.7)}$$

- Incremental cost (IC): the difference in costs between two or more interventions in an evaluation, defined as

$$IC_{AB} = TC_A - TC_B \quad \textbf{(1.8)}$$

In cost estimation, an initial consideration is whether to use average or marginal costs; however an important difference is that fixed costs are included in average costs, but not in marginal costs. [83] Therefore, the inclusion of average costs or marginal costs is often down to the research question, but economic evaluation of healthcare technologies are often interested in evaluating interventions which may have long term costs and effects, and therefore tend to favour average costs. With the incremental approach, the evaluation estimates both the total costs associated with the intervention and its comparator, and hence an incremental cost is calculated, although these costs are often shown as an average cost per patient.

In economic evaluation, there are currently two common approaches to measuring and calculating total costs for an intervention and its comparator; bottom-up micro-costing and top-down macro-costing. [84] The top-down macro- (gross) costing approach can be seen as the least precise [33], as it uses the average per diem across all categories of patient,

with a slightly more precise version involving disease-specific per diem across the treatments in each disease category. The advantage of macro-costing is that it is relatively easy to undertake and can often be calculated using routinely available data, but it can lack sensitivity. [84] Bottom-up micro-costing refers to the detailed analysis of changes in resource used due to the intervention. [33] This can involve multiplying each component of resource use by its associated price (if it exists) or reimbursement cost, which can be difficult to undertake, computationally demanding and complex, and possibly only generalizable to specific contexts. [84] However, if prices do not exist or are not considered to reflect society's values of resources, this may require customised work, further affecting the generalisability of the cost estimates. [85] In practice, researchers often use a combination of macro- and micro-costing when performing an evaluation to produce the best available estimates of costs of the intervention and its comparator. In the UK, the NICE reference case does not specify whether a macro- or micro-approach is used [36]; however, it does recommend that researchers use cost data collected as part of routinely collected data, such as the NHS Drug Tariff and the British National Formulary for medications and prescriptions [86, 87], and NHS reference costs for healthcare resource groups (HRGs). [88]

A further consideration for costs is that an evaluation must report the price year for which the costs were calculated. [43] This allows replication of the evaluation in the future. When using costs from the literature, they are often from an earlier price year, and need to be updated to account for medical price inflation. This is done using one of the price inflation indices, for example the Hospital Pay and Prices Index in the UK and the Consumer Price Inflator in the US. [89, 90] To inflate costs to a particular year, the following equation can be used [89]:

$$Cost_{New\ year} = Cost_{Old\ year} \times \frac{Index_{New\ year}}{Index_{Old\ year}} \quad \textbf{(1.9)}$$

For example, if an evaluation is conducted using 2011-2012 prices, and used an estimate for a particular disease reported in in 2004-2005 prices to cost £500, using the Hospital Pay and Prices Index this figure can be inflated to 2011-2012 prices thus:

$$Cost_{2011-2012} = £500 \times \frac{282.5}{232.3} = £500 \times 1.2161 = £608.50 \quad \textbf{(1.10)}$$

Hence, £500 in 2004-2005 is now £608.50 in 2011-2012 prices, and this value is used in the model. Future price inflation is not considered when estimating future costs [83], however future costs are discounted, as considered in the next section.

1.6.6 Discounting

Interventions may have costs and consequences which occur at different times, and hence the differential timing must be taken into account. [33] Economists assume that individuals have a positive rate of time preference; that is we prefer to receive benefits now and incur costs in the future. [91] This is assumed because individuals have a short-term view of life, preferring to live for today rather than tomorrow; that the future is uncertain so people prefer to take the certain benefits now; and finally individuals expect to be more wealthy in the future so money today is of higher value than money in the future. [33] Hence, it can be assumed, under a positive rate of time preference, individuals must value future costs less than they do now (so a £100 bill in ten years' time must have less value than £100 bill now) and that any future benefits must be valued less they do now (so a £100 gift must have more value now than a £100 in ten years' time). Discounting future costs and benefits is achieved by applying a discount rate *r,* to calculate the present value of a future cost [33]:

$$PV = \frac{F_n}{(1+r)^n} \qquad \textbf{(1.11)}$$

$$where\ PV = present\ value, F_n\ is\ future\ cost\ at\ time\ n, r = discount\ rate$$

Total discounted future costs can be calculated using this approach; however the equation is slightly different whether the costs are being attributed at the end of the year or the beginning of the year. [33] For costs attributed at the end of the year, the total present value of future costs can be calculated thus:

$$\sum PV = \sum_{n=1}^{n} F_n(1+r)^{-n} = \frac{F_1}{(1+r)} + \frac{F_2}{(1+r)^2} + \cdots + \frac{F_n}{(1+r)^n} \qquad \textbf{(1.12)}$$

$$where\ PV = present\ value, F_n = \ future\ cost\ at\ time\ n,$$
$$r = discount\ rate$$

For costs attributed at the beginning of the year, the total present value of future costs can be calculated thus:

$$\sum PV = \sum_{n=0}^{n} F_n(1+r)^{-n} = F_0 + \frac{F_1}{(1+r)} + \cdots + \frac{F_n}{(1+r)^n} \quad \textbf{(1.13)}$$

$$where\ PV = present\ value, F_n = future\ cost\ at\ time\ n, r = discount\ rate$$

While discounting future costs is considered uncontroversial, there is considerable debate as to whether to discount future benefits. [91] The main argument against discounting future benefits is that health cannot be invested to produce future gains, unlike wealth, which can. Furthermore, the process of discounting could be seen as discriminating against preventative and public health programmes, where many of the benefits are gained a long time in the future. [92] However, one argument against not discounting future benefits is the Keeler-Cretin paradox, which suggested that if you discounted costs and not benefits, then certain interventions would be indefinitely postponed because they would always be cheaper in the future and have the same effectiveness. [93] Furthermore, there is evidence to suggest that certain individuals discount health benefits more, for example smokers tend to value future health benefits less than non-smokers. [94] Because discounting future costs and benefits can have such an impact on the evaluation's decision, it is now considered good practice to perform sensitivity analyses on the discount rate to determine what impact the discount rate has on the results. [43] The NICE reference case recommends that for the UK both costs and benefits should be discounted at 3.5%, with a sensitivity analysis performed on 1.5%.

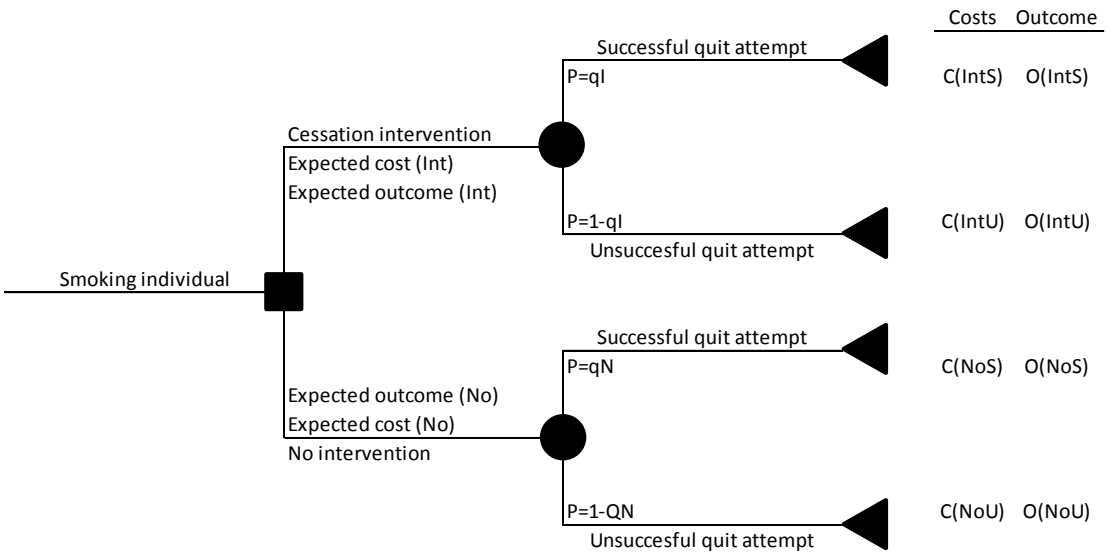
1.6.7 Decision analytic modelling in economic evaluation

As has been previously mentioned, this thesis will be focusing on the use of decision analytical models in economic evaluation. There are many decision analytic methods which can be used in economic evaluation; however, this thesis will focus on the two most common methods, decision trees and Markov cohort simulation. This section will briefly outline each approach, when they are appropriate, and the limitations of the approach, as well as briefly summarising the alternative methods.

1.6.7.1 Decision Trees

A decision tree is considered the simplest form of model. It represents an individual patient's possible prognoses after an intervention as a series of pathways, referred to as branches. [33, 41] For example, an evaluation is being performed on a hypothetical smoking cessation intervention compared to no intervention. For simplicity, it assumed that an intervention can either make a successful or unsuccessful quit attempt, with the intervention only affecting the chance that a quit attempt is successful. This scenario can be represented in a decision tree, as demonstrated in Figure 1.1.

Figure 1.1: An example decision tree for a hypothetical smoking cessation intervention



The decision tree demonstrates the four possible pathways: use the intervention and successfully quit, use the intervention but be unsuccessful in quitting, don't use the intervention but successfully quit, and don't use the intervention and be unsuccessful in quitting. Each pathway has associated pay-offs on the right hand side, representing the costs and benefits (in this example termed outcomes). From Figure 1.1 it can be seen that there are three types of nodes, which can be defined as (from right to left):

- Terminal node (triangle): these represent the end of the pathways, and are linked with the associated payoffs, namely costs and benefits

- Chance node (circle): these represent a situation where an individual could potentially move to at least one of two or more branches. Here the individual/decision maker has no control over what happens to the individual, it is an uncertain event, so the pathway is chosen by a probability. A probability is a value which represents the chance (or confidence) that an event occurs. [95] The alternatives at each chance node must be mutually exclusive (cannot occur at the same time), hence the associated probabilities for each node must sum to one
- Decision node (square): a node where the individual can choose which path to take, e.g. use the intervention or not

To perform the evaluation and to determine whether the intervention is worth using, the decision tree is rolled back from right to left. This requires the calculation of the expected costs and outcomes for both the intervention and no intervention arms. The expected costs and outcomes for the intervention arm are calculated thus:

$$Expected\ cost\ (intervention) = \big(qI \times C(IntS)\big) + \big((1 - qL) \times C(IntU)\big) \quad \textbf{(1.14)}$$

$$Expected\ outcome\ (intervention) = \big(qI \times O(IntS)\big) + \big((1 - qI) \times O(IntU)\big) \quad \textbf{(1.15)}$$

$$where\ qI = probability\ of\ successfully\ quitting,$$

$$C(IntS) = total\ cost\ of\ intervention\ plus\ cost\ of\ a\ successful\ quit\ attempt,$$

$$C(IntU) = total\ cost\ of\ intervention\ plus\ cost\ of\ a\ unsuccessful\ quit\ attempt$$

$$O(IntS) = benefit\ associated\ with\ a\ successful\ quit\ attempt,$$

$$and\ O(IntU) = benefit\ associated\ with\ a\ unsuccessful\ quit\ attempt$$

The expected costs and outcomes for the no intervention arm are calculated using the same equations above, just adjusting the parameters and payoffs to suit the no intervention arm. Once this is complete, it is now possible to determine which arm offers more value for money; how this is determined is introduced later in this chapter.

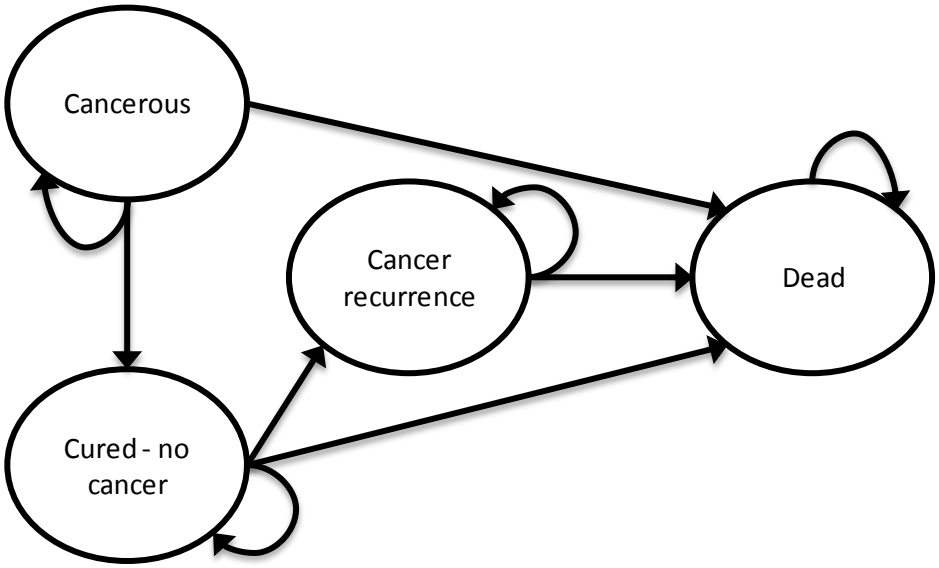
The advantage of the decision tree is that it is very simple to build and evaluate, and can be very transparent/easy to interpret for non-economists. [41] It lends itself to situations where there is no time dependency, or the patient follows a logical flow, e.g. being diagnosed, treated, and cured or dead. [41] However, there are several limitations with the

decision tree approach. Firstly, decision trees implicitly assume that events occur over an instantaneous discrete period. [33] This means that time is not explicitly defined, and hence elements of the evaluation which rely on time such as discounting are very difficult to implement. Secondly, a decision tree can very quickly become complex, referred to as bushy, when dealing with long-term prognoses, such as chronic diseases. [33] Decision trees do not allow recursion to a previous branch (looping), which means that each relapse in a chronic disease has to be built in as separate branches. [41] If following a disease for many years, this could very quickly to lead to a decision tree which has thousands of branches, and consequently a model which would be very time consuming to populate and evaluate. Hence, decision trees are not used for modelling long-term follow-ups or chronic conditions.

1.6.7.2 Markov cohort simulation models

To address the limitations of decision trees, Markov models use a more straightforward and flexible approach, where patients are allowed to occupy a series of 'states' at any given point in time. [33, 39, 41] The model runs in cycles, which represent a discrete time period (e.g. one year, six months, etc), and in each cycle patients can transition from one state to another. The chance that a patient transits to another state, or remains in the state they are in, is determined by the transition probability, which is defined in the evaluation. The number of cycles that the model runs for and the length of each cycle is determined by the research question; for example a model investigating the treatment of dyspepsia (indigestion) may use one month cycles to capture the frequent relapses associated with the disease, while a model for lung cancer survival may use six month cycles because of the slow rate of relapse. A model can either be run for a set number of cycles, or can be run until all the individuals have entered the absorbing state. An absorbing state represents a state which individuals can enter but not exit. In healthcare related Markov models, this state often represents death. Markov models are often used in cohort simulation, whereby a number of individuals (e.g. 1,000) are fed into a particular health state at the start of the model, and then allowed to cycle through the various health states, allowing the model to calculate the number of individuals in each health states in any given cycle. Figure 1.2 demonstrates a simple Markov model of a chronic disease, e.g. cancer.

Figure 1.2: A simple Markov model of cancer



In Figure 1.2, a patient could start off by being cancerous, receive treatment and transit to being cured, remain without cancer for some time (i.e. remain in the cured state for several cycles), before the cancer recurs, and then eventually die. The probability that an individual will move states can be represented by the following transition matrix:

Table 1.1: Transition matrix for the Markov in Figure 1.2

	Transit to			
Transit from	Cancerous	Cured – no cancer	Cancer recurrence	Dead
Cancerous	R	P(Cure)	0	P(Mortality from cancer)
Cured – no cancer	0	R	P(Recurrence)	P(Mortality no cancer)
Cancer recurrence	0	0	R	P(Mortality recurrence)
Dead	0	0	0	1
R = remainder; all rows should add up to one, e.g. in Cancerous row, R = 1 – P(Cure) – P(Mortality from cancer)				
P = probability of transit				

The transition matrix demonstrates that death is the absorbing state, as individuals who enter are never allowed to exit. The transition matrix also demonstrates that once a patient

has had a cancer recurrence, they cannot transit back from being cured, which suggests that this model is assuming that recurrence can only happen once. Furthermore, all rows in the transition matrix should sum to one, and to allow for this, it is good practice to denote a particular transition to be one minus the other probabilities in the row, which in this model is the probability of remaining within the cycle. In addition to the normal state (where individuals can remain in the state for more than one cycle) and the absorbing state, there is the additional tunnel state. A tunnel state represents a state in which an individual can only remain for one cycle. At the end of that cycle, they must transit to another state; they cannot remain in the tunnel state.

As mentioned, in each cycle the number of individuals in all the states is calculated. Each state can be given a particular cost and benefit. Hence the total cost and benefit in each cycle can be calculated by multiplying the number of individuals in a particular state by its associated cost/benefit, and then summing the same calculations for all the states. The total cost/benefit per patient can then be calculated by summing the associated costs/benefits for each cycle, then dividing this value by the number of individuals in the cohort. To model the impact of an intervention, the transition probabilities can be changed to represent the effect the intervention has on the patients moving states. For example, a new intervention could change the associated probability values for P(cure) and P(recurrence), which would then affect the expected costs/benefits per person.

The advantages of the Markov model approach is that it is now easy to build in parts of the evaluation which are reliant on time, e.g. discounting. [33] Discounting can easily be achieved by weighting each the costs and benefits in each cycle by the discount rate. Additionally, the Markov has simplified what would have been a very bushy decision tree for the cancer situation into a relatively small Markov model with only four states. [41] Because of this, Markov models are particularly useful if modelling long-term time horizons (e.g. lifetime), or chronic diseases which may have a lot of looping between states.

However, there is an important limitation associated with the Markov model, which is referred to as the Markov assumption. The Markov assumption states that the transition probabilities for a health state depend only on that state and not on the historical

experience an individual may have had in previous cycles of the model; in other words the model is memoryless. [41] For example, in the Markov model demonstrated in Figure 1.2, the chance that a cured individual transits to having a recurrent cancer is the same, independent of whether the individual has been in the cured state for one cycle or a 100 cycles. Although it is possible to work around the Markovian assumption using additional states to represent historical outcomes, it can quickly mean that the Markov model becomes as unwieldy as the decision tree that it was designed to replace. [33] Therefore, if transit probabilities are dependent on the previous state history of the patient, then a Markov model might not be appropriate for performing the evaluation.

1.6.7.3 Alternative methods in decision analytic modelling

Although Markov models and/or decision trees are the most common forms of modelling in economic evaluation, there are several alternatives. Some of these are:

- Patient level simulation (microsimulation): models the progression of individuals through the healthcare process. [41, 96] Individuals in the simulation have potentially heterogeneous characteristics that can affect the progression through the model. However, they are allowed to progress through the model independently of each other and environmental constraints. These individual microsimulations allow individuals to progress while keeping a track of the history of which nodes that the patients progress through, which is useful if probabilities, costs, and benefits are reliant on the previous history of the individual. [96] This allows the model to include the impacts of several co-morbidities, while allowing them to interact with each other. Furthermore the model does not necessarily have to rely on an equal discrete time cycle, but could use time to next event. However, the limitations with the microsimulation approach are that they are heavily reliant on the parameters for future prognoses, which may be difficult to populate within the limitations of the available data. [33] Furthermore, controlling for uncertainty in the model is computationally intense and can be time consuming.[33]
- Discrete event simulation: models the progress of a group of individuals through the healthcare process, allowing for impacts from an individual's characteristics and outcomes, as well as allowing for individuals to interact with each other, e.g.

an individual's decision not to donate an organ can impact on whether another can receive a transplant. [41] Discrete event simulation has no fixed time cycle, rather patients change states when an event occurs, which then in turn may impact on the chances of a patient having a subsequent event. [96] This type of model is particularly useful when there is non-linearity in the healthcare system performance due to inherent variability within patients, such as infectious diseases. [96] However, discrete event simulation suffers from similar limitations as microsimulation, such as availability of data to populate the model, and computational slowness. [96]

- Dynamic models: these models allow interaction between patients without separating individuals. [96] The models work on the basis that the states of the system can change, and that the rate of change can be a function of the system's state itself, hence the model allows feedback. This is particularly useful for infectious diseases, where higher levels of infection can increase the risk of infection but also reduce the number of individuals in the susceptible pool. [96] However, these models can be incredibly complex, especially if the decision problem is complicated and not all the relationships are established. [97]

1.6.8 Statistics for the comparison of interventions and rules for decision making

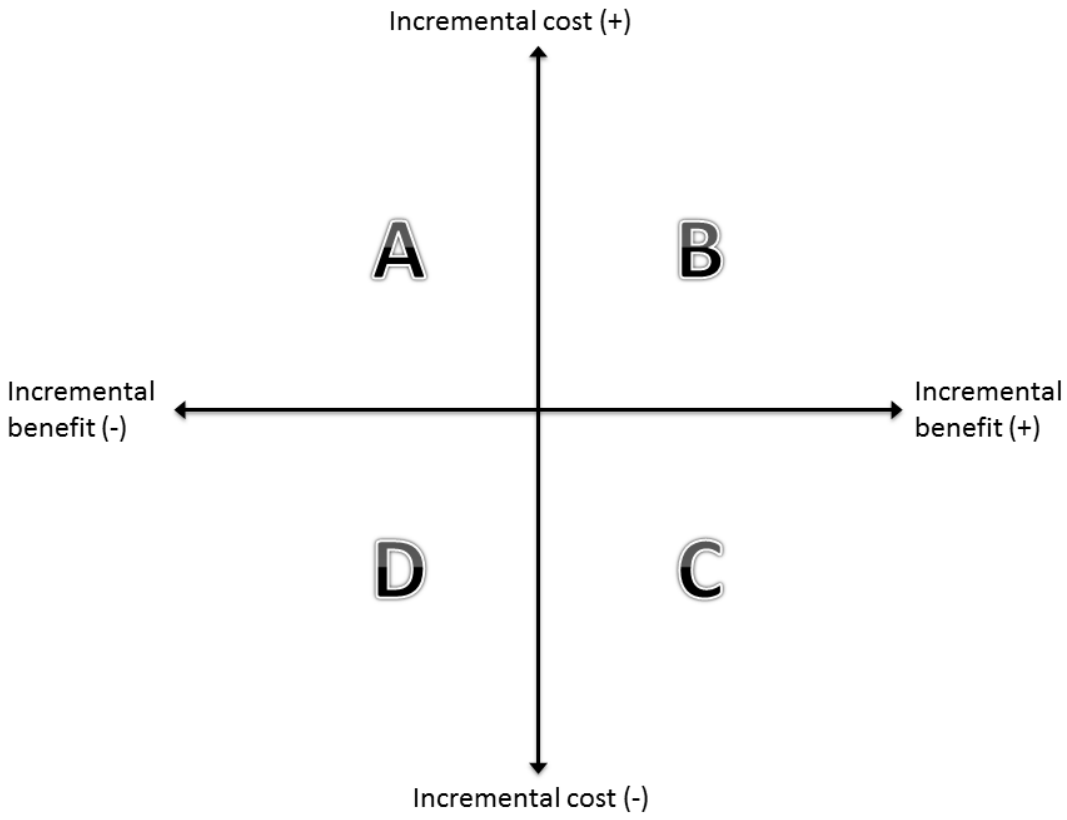
To be able to determine whether an intervention is cost-effective or not, an incremental analysis is required. [33] Although it is possible to calculate the average cost-effectiveness (ACER, $ACER = \frac{E(cost)}{E(outcome)}$), an ACER does not generate the comparative information required to determine whether an intervention is cost-effective compared to its comparator. [33]One of the outputs of decision analytic models (DAMs) is the expected costs and expected outcomes (benefits) associated with each intervention being evaluated. Hence, we can calculate the incremental cost and benefit of the new intervention thus:

$$Incremental\ Cost = Expected\ cost_{New\ intervention} - Expected\ cost_{Comparator} \quad \textbf{(1.16)}$$

$$Incrmental\ Benefit = Expected\ benefits_{New\ intervention} - Expected\ benefits_{Comparator} \quad \textbf{(1.17)}$$

One way to evaluate the results is to plot the incremental costs and benefits on the cost-effectiveness plane, which is demonstrated in Figure 1.3.

Figure 1.3: The cost-effectiveness plane



The cost-effectiveness plane can be divided into four regions; A, B, C, and D. If the incremental costs and benefits for the new intervention are plotted in region A, the new intervention is said to be dominated by usual care. This is because the new intervention is more expensive and less effective than usual care, and hence it would be unnecessary to perform an evaluation since it would be illogical to introduce the new intervention. However, if the incremental costs and benefits for the new intervention are plotted in region C, the opposite situation exists. In region C, the intervention is more effective than usual care, and is cheaper in terms of healthcare costs, therefore the new intervention can be said to dominate usual care. Again, it would be unnecessary to perform an evaluation here as it is logical to choose the new intervention, since it is better than usual care. However, in regions B (where the new intervention is both more effective and more costly

than usual care) and D (where the new intervention is cheaper than usual care but less effective), it cannot be determined whether the new intervention is dominant over or dominated by usual care, and hence it is necessary to determine if the new intervention weakly dominates usual care.

One method to determine weak dominance is to calculate the incremental cost-effectiveness ratio (ICER). [33] This is the ratio of incremental costs over incremental effectiveness. The equation for the ICER is:

$$ICER = \frac{E(cost)_{new\ intervention} - E(cost)_{usual\ care}}{E(outcome)_{new\ interventon} - E(outcome)_{usual\ care}} \quad \textbf{(1.18)}$$

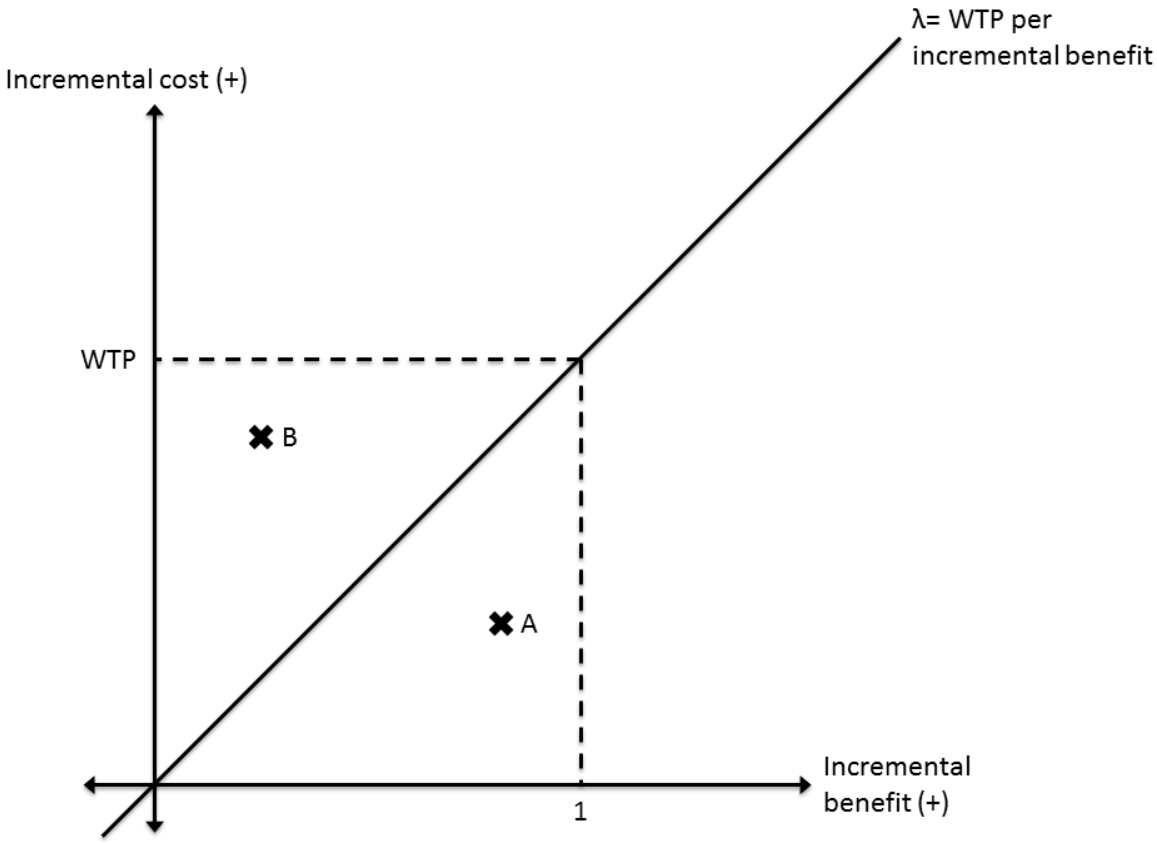
In regions B and D, the ICER will return a positive value; however in regions A and C it will return a negative value, which is very difficult to interpret, hence it is best practice not to report the ICER if the intervention appears to be dominant or dominated. To determine whether the intervention weakly dominates usual care, a decision rule is required. This can be represented as [98]:

$$We\ accept\ the\ new\ intervention\ if\ the\ ICER \leq \lambda$$

$$where\ \lambda\ represents\ our\ willingness\ to\ pay\ for\ additional\ one\ unit\ gain\ in\ benefit$$

This means that if the ratio of incremental costs and benefits is less than or equal to what a policy maker is willing to pay for an additional one unit gain in benefits, then the new intervention could be deemed as cost-effective, or value for money. This threshold value can be represented on the cost-effectiveness plane by a straight line passing through the origin and a point representing a one unit increase in benefit and the threshold value, as can be seen in Figure 1.4 below, with point A representing a intervention where the ICER is less than the threshold value.

Figure 1.4: The threshold value on the cost effectiveness plane



If the ICER is above λ (e.g. point B in Figure 1.4), then the new intervention cannot be deemed cost-effective and usual care would be the treatment of choice. The λ represents the policy maker's threshold value, i.e. what the policy maker is prepared to sacrifice for a one unit gain in benefit. What this value is and how it is calculated is discussed further later in this chapter. Although the point estimate for an ICER is relatively easy to compute, because it is a ratio statistic, the variance is not defined. This makes computing the confidence interval around the ICER problematic, although this can be addressed to some extent using non-parametric bootstrapping for within-trial analyses and probabilistic sensitivity analyses (PSAs) in models. [99] In decision modelling, the model can be programmed to use the ICER to determine which option to choose at each decision node.

An alternative to the ICER is the incremental net monetary benefit statistic (INB). This is the incremental difference between the net monetary benefit for each intervention (NMB).

The NMB can be calculated by [99]:

$$NMB = (\lambda \times E(outcome)_{Intervention}) - E(cost)_{Intervention} \quad \textbf{(1.19)}$$
$$where\ \lambda = the\ policy\ maker's\ threshold\ value$$

Hence, the INB can be calculated by taking the difference in the NMB between the new intervention and usual care:

$$INB = NMB_{New\ intervention} - NMB_{Usual\ care} \quad \textbf{(1.20)}$$

It is also worth noting that the INB is a rearrangement of the ICER, and hence can be defined as:

$$INB = \big(\lambda \times (E(outcome)_{New\ intervention} - E(outcome)_{Usual\ care})\big) \quad \textbf{(1.21)}$$
$$-(E(cost)_{New\ intervention} - E(cost)_{Usual\ care})$$

The decision rules for the INB are quite simply [39]:

$$we\ reject\ the\ new\ intervention\ if\ the\ INB < 0$$

$$we\ are\ indifferent\ about\ the\ new\ intervention\ if\ the\ INB = 0$$

$$we\ accept\ the\ new\ intervention\ if\ the\ INB > 0$$

This makes the INB very easy to interpret, since a positive monetary figure suggests that there is a net benefit from the new intervention and hence it should be adopted, while a negative value suggests there is a net loss and therefore that the new intervention shouldn't be adopted. The advantage of the INB is that since it is not a ratio statistic, it is now possible to fit a confidence interval on the point estimate. [100] In decision analytic models, it is more common for the model to use the NMB statistic rather than the ICER since it is assumed we will always attempt to maximise benefits. [39] For example, if a decision node had three choices, and all of which had an ICER below the threshold value, the model faces a complex decision process. However, if the model calculates the NMB for each intervention, it can then easily choose whichever offers the highest NMB.

1.6.8.1 Determining the policy maker's threshold value

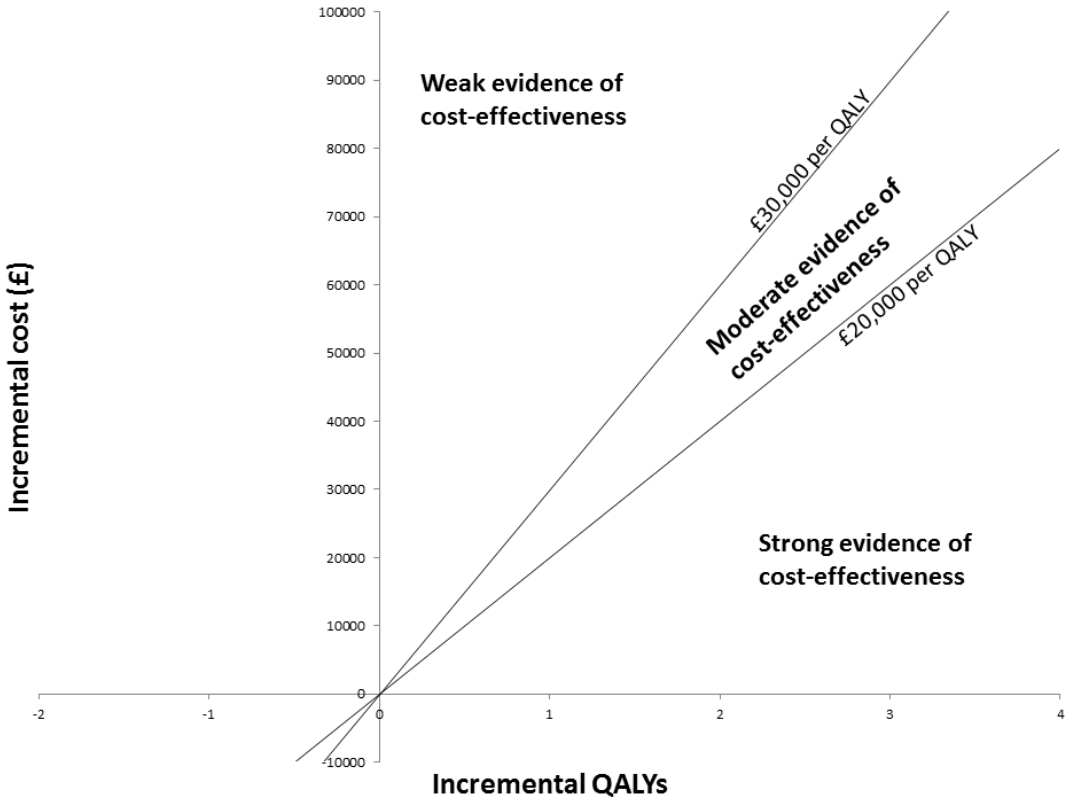
For a decision maker to determine whether a new intervention offers value for money, they must compare the ICER with a threshold value, i.e. a value which represents their willingness to pay for health gain. [54] In countries with a state-funded healthcare system like the UK, this is particularly important since they often practise healthcare rationing within a finite budget. [101] Although there are many ways a decision could be made, e.g. allowing doctors to choose what they think is best; first come first served basis, these approaches could be argued to not only be unfair/discriminatory to certain individuals but could also lead to inefficiency, hence wasting the scarce resources that the decision maker is seeking to prolong. [76, 101] It can also be argued that the threshold value reflects society's perceived opportunity cost, demonstrating what society is prepared to sacrifice to gain some additional benefit, and that the ICER represents the value judgement; the value for money of the intervention. [33, 34]

In the UK, the governing body NICE is responsible for determining the availability of interventions/treatments on the NHS. Part of its remit is to determine whether the new intervention/procedure offers value for money, and hence has a threshold value reported in incremental cost per QALY. The current NICE guidance states that this threshold is [36]:

- ICER<£20,000 per QALY: strong evidence of cost-effectiveness given the acceptability of the technology to the NHS. An intervention with a ICER below £20,000 per QALY will only be rejected if the committee does not believe the plausibility of the evaluations inputs or the uncertainty surrounding the ICER
- £20,000 per QALY≤ ICER <£30,000 per QALY: moderate evidence of cost-effectiveness. Decision will rely on the certainty around the ICER, whether changes in health-related quality of life have been adequately captured, the innovative nature of the technology and whether it adds demonstrable and distinctive benefits which may not have been captured by QALYs, or whether the treatment has special considerations for palliative care
- £30,000 per QALY ≤ ICER: weak evidence of cost-effectiveness. The committee will need very strong evidence for the new technology

The NICE threshold values can be represented on the cost-effectiveness plane, as demonstrated in Figure 1.5.

Figure 1.5: NICE threshold values for determining cost-effectiveness of new technologies and interventions, as presented on the cost-effectiveness plane



Initially, NICE denied that it was applying these threshold values, and argued that it was down to the individual decision committees to determine whether or not an intervention was considered cost-effective. However, Devlin et al used a discrete choice analysis to elicit that the threshold was estimated at £20,000 - £30,000 per QALY, although there was evidence that it may be higher. [102] The NICE threshold value has been criticised, with the initial behaviour of NICE not stating the threshold value being described as opaque, and that it was considered to be too high. [103] However, some have argued that it is not NICE's constitutional role to determine the value of an additional QALY, as that is a role for politicians, and that NICE's purpose is to search for the threshold implied by the prevailing NHS budget. [104] However, more recent literature has continued to investigate the value of the threshold. Claxton et al performed an econometric analysis on changes in healthcare

expenditure and its impacts on mortality and QALY gains, to give a best estimate of the NICE threshold. [34] The analysis returned a value of £12,936 per QALY based on 2008 expenditure, and when controlling for uncertainty, the probability that the threshold was below £20,000 per QALY was 0.89 and below £30,000 per QALY was 0.97. However, the authors acknowledge that due to assumptions, it was difficult to infer whether the £12,936 per QALY threshold was an underestimate or an overestimate of the true threshold value. Despite this, they concluded that it was more likely than not that the value was an overestimate, and the true value was likely to be somewhat lower. However, this work has been brought into question, with Barnsley et al suggesting that, in reality, Claxton et al are underestimating the threshold value. [105] Barnsley et al highlight that, firstly, the central threshold estimate of £12,936 per QALY is highly sensitive to the assumption that the unexplained 28% of primary care trusts budgets is distributed according to the estimated responsiveness to changes in budget, and that relaxing this assumption drives the estimate up to £18,317 per QALY. Furthermore, Barnsley et al argued that, regarding the uncertainty, the evidence suggested that although there was a smaller probability that the threshold had been substantially underestimated than slightly overestimated, there was almost no chance that it had been substantially overestimated, suggesting that Claxton et al's conclusions that the threshold value was too high to be incorrect, and that in reality it was more likely to be higher and in line with the current NICE reference case. [36] More recently, Schaffer et al attempted to estimate the cost-effectiveness threshold in Scotland by investigating services which had just received, or were about to receive, investment in 2012/13, and by comparing these figures with literature based estimates for QALY gains, calculate the implied threshold. [106] They found that there was a great deal of uncertainty in the QALY threshold, with the median threshold across the several services estimated to be £1,516 to £1,017,844 per QALY gained. However, the authors identified that in none of the decisions was cost per QALY data used, which may explain why there was such variation in the threshold value.

Despite the discussion on the value of the NICE threshold, it is important to realise that the value is there to prevent inefficient treatments being funded, as they can imply a cost to not only the NHS but to society as a whole. Every approval has a so-called opportunity cost, and it is important that NICE is able to determine which new technologies are going to have a minimal opportunity cost across the healthcare system. For example, Claxton et al

highlighted that in 2011 NICE considered whether ranibizumab should be approved for widespread use for the treatment of diabetic macular oedema, and initially rejected the technology on the grounds that it was unlikely to be cost-effective [34], with an ICER of £19,075 in the base case, and the probability of being cost-effective at £20,000 per QALY of 49.3%. [107] The appraisal of ranibizumab estimated that it would cost the NHS £80millon per annum to treat the eligible population. [34, 107]Assuming that budget was finite, money earmarked for other treatments would need to be transferred from other disease areas, with Claxton et al estimating that the funding of ranibizumab would have displaced 6,184 QALYs from elsewhere in the NHS, including 411 additional deaths and 1,864 life years foregone. [34]

More recently, Schaffer et al investigated how NHS organisations which could be considered to have fixed budgets accommodated financial shocks arising from NICE technology appraisals, and how prioritisation decisions were made in the NHS by those budget holders. [108] The authors focused on the seven local health boards in NHS Wales, with semi-structured interviews. The authors found that the majority of NICE recommendations were anticipated by using horizon scanning, which created contingency funds which were adequate enough to cover the extra expenditure in that financial year. There was little evidence of service displacement, but there were signs that some of the additional funds came from improving efficiency, though there seemed to be an equal spread amongst local health boards as to whether efficiency savings came from the same disease area of the new technology or from the medicines' budget as a whole. However, on occasion the Welsh government stepped in as the funder of last resort, suggesting that the part of the opportunity cost may be outside the NHS. Compared to the work by Claxton et al [34], Schaffer et al have implied that the opportunity cost is already anticipated, and hence doesn't lead to the QALYs lost as suggested by Claxton et al; however, part of it lies outside of the NHS. [108]

1.6.9 The role of uncertainty and its impact on economic evaluation

An important requirement for economic evaluation in terms of decision making is to indicate how uncertainty in the available evidence translates into decision uncertainty, i.e.

the probability that the recommended decision is the correct one. [39] It has been argued that controlling for uncertainty is as important as assessing the deterministic cost-effectiveness estimates. [109, 110] Uncertainty matters because it is important to provide correct evaluation of expected cost and effect, to consider whether current evidence is sufficient, and to estimate the possible consequences of an uncertain decision for the NHS. [110] There are several key concepts in uncertainty, and several approaches that can be used to control for it:

- Variability: Individual patients differ from one another (e.g. clinical events they experience, health related quality of life, risk of disease). [39] Cannot be reduced through the collection of additional data. [39]
- Parameter uncertainty: The precision associated with input parameters (probability of event, mean costs, utility values). [39] This imprecision is a result of the input parameters estimated for a population from the best evidence available. In theory, can be reduced by the acquisition of further data. This can be controlled for by using probabilistic sensitivity analyses, which is discussed in detail later in this section.
- Heterogeneity: The extent of inter-patient variability in a particular measurement on the basis of one or more patient characteristics, (e.g. the risk of a disease may be higher in men). [39] This can be controlled for with sub-group analysis allowing for decision uncertainty for particular patient characteristics; however parameter uncertainty will still exist.
- Structural uncertainty: Refers to the impact of the assumptions made to simplify the complex healthcare process and prognoses that patients can experience. [33]These judgements on the appropriate structure of the model can have important impacts on the results of the analysis. Two methods exist to control for structural uncertainty; model averaging, where alternative models are constructed with different specifications, and the results averaged; and model selection on the basis of prediction performance or appropriateness. [111, 112]
- Methodological uncertainty: The choice of model used to perform the evaluation may engrain a series of structural assumptions, making controlling for structural uncertainty difficult. [33] This may require the construction of two models using two different methods (e.g. Markov simulation versus microsimulation), however it is difficult to undertake, and this puts the decision maker in the position of also deciding which is the most appropriate model. [33]

- Decision uncertainty: The distribution of possible cost-effectiveness estimates due to parameter uncertainty. [39] There is a strong argument for basing decisions on the expectation of this distribution, as it demonstrates the confidence the researchers have in the decision being the correct one. [39, 109] Providing evidence of decision uncertainty is now an important part of the NICE reference case.[36]

1.6.10 Controlling for parameter uncertainty

There are several approaches for controlling for parameter uncertainty. One approach is to use one-way sensitivity analyses. [33] This involves varying a parameter through a plausible range of values, though it is possible to vary two parameters at a time. [33] Although these deterministic approaches to demonstrate uncertainty are still considered useful for demonstrating the sensitivity of the ICER [112], the deterministic approach has been criticised in that it only allows a small number of parameters to vary, which could be considered unrealistic; there is no control for correlation between input parameters, and it does not produce a summary measure of the implications of uncertainty. [33, 109]

An alternative approach to deterministic sensitivity analyses is to use a probabilistic sensitivity analysis (PSA). [39] In decision analytic modelling, this involves placing suitable distributions on the input parameters within the model, then repeatedly sampling the input parameters using Monte Carlo Simulations to produce a distribution of expected incremental costs, expected incremental benefits, and the associated ICER. [39] For within-trial analyses, PSAs involve randomly sampling the incremental costs and benefits using non-parametric bootstrapping. [40] The number of iterations performed in either the bootstrapping or Monte Carlo simulation should be enough that the estimates reach stability, and hence it has been recommended that at least 1,000 replications should be performed to produce reasonable estimates for confidence interval calculation. [100] There is no given rule as to the number of iterations required, but it is considered good practice to determine whether the analysis has achieved stability. [113] This can be investigated by repeatedly running the analysis from a small number of bootstraps (e.g. 10) to a large

number (e.g. 5000) to determine whether stability has been achieved in the expected estimates for the mean and standard error of the ICER. [113]

There are several distributions that can be used for fitting to parameters to perform a PSA. It is recommended that distributions are fitted to all parameters within the DAM [112], however when finding the appropriate information for a particular parameter, a mean is reported but not a standard error or other estimate of uncertainty. In these situations, it is good practice that some conservative estimate for the standard error is used [112], and therefore in this thesis a 10% error is used as per practice of several other models. [114-116] Some of the most common distributions used in economic evaluation are:

- Normal distribution($X \sim Norm(\mu, \sigma)$): A common continuous probability distribution, with mean μ and variance σ^2. [39] The normal distribution is useful due to the central limit theorem, which states that the sampling distribution of the mean is normally distributed irrespective of the underlying distribution of the data if there is sufficient sample size. [39] Hence, if the dataset being used for a particular parameter is of a large enough size, the normal distribution can be used to sample this value. However, if the dataset is not large enough, or the information for a particular parameter is a single estimate (e.g. proportion smoking from national statistics), the normal distribution cannot be used. [39] Furthermore, the normal may sample values outside the plausible range of the parameter, for example a normal distribution fitted to a probability could in theory sample a value greater than one, which is impossible for a probability. [39] Hence we have to use an alternative distribution.
- Beta distribution ($X \sim Beta(\alpha, \beta)$): A continuous probability distribution defined on the interval$[0 - 1]$, which can partition the interval into two parts. [39]The Beta distribution is used in Bayesian statistics for representing a probabilistic distribution of probabilities and proportions. It will return values for x such that $0 < x < 1$. The distribution is parameterised using two positive shape parameters α and β, such that the distribution has mean $\frac{\alpha}{\alpha+\beta}$ and variance $\frac{\alpha\beta}{(\alpha+\beta)^2(\alpha+\beta+1)}$. This means that the Beta distribution is flexible, and allows us to change the shape of the distribution easily. The Beta distribution is used to sample the values for probabilities where there are only two possible outcomes (e.g. success or failure), and for utility weights. [39]

- Dirichlet distribution ($X \sim Dir(\alpha)$): A continuous multivariate probability distribution, parameterised by the vector α and the number of categories, K, which is defined on the interval $[0 - 1]$, splitting the interval into two or more parts. [39]The number of categories must be such that $K \geq 2$, and that $\alpha_1, \cdots \alpha_K$ are the concentration parameters, where $\alpha_i > 0$. The Dirichlet distribution will return values x such that $x_1 + \cdots + x_i = 1$. This is the multivariate generalisation of the beta distribution. The Dirichlet distribution is often used when sampling probability values where there are more than two possible outcomes. [39]
- Gamma distribution ($X \sim \Gamma(\alpha, \beta)$: A continuous probability distribution defined on the interval $[0 - \infty]$, parameterised by a shape parameter α and a rate parameter β. [39] Because the Gamma distribution is bounded by zero, and is right-skewed, it can be used to sample x such that $x > 0$. The Gamma distribution has mean $\alpha\beta$, and variance $\alpha\beta^2$. In Bayesian statistics, the Gamma distribution has a special relationship with Poisson data because it is conjugate to the Poisson distribution, and therefore can be used to characterise Poisson data. The Gamma distribution is used when sampling costs since these are also right-skewed and costs data is often based upon Poisson data. [39]
- Lognormal distribution: A continuous probability distribution of a random variable whose logarithm is normally distributed. [39] The distribution is parameterised by μ and σ, which are the mean and standard deviation of the variable's natural logarithm. The Lognormal distribution is used for sampling occurring variables that are the product of a number of other occurring variables. Since odds ratios (OR) and relative risks (RR) are the products of the number of people who develop a disease contingent of exposure, it would seem appropriate to assume the ORs and RRs are Lognormally distributed, hence the Lognormal distribution is used to sample ORs and RRs. [39]

Both the Beta and the Gamma distributions require the distribution to be fitted. For the Beta distribution, there are two approaches. One approach is to specify the shape parameter α as the number of times the event has occurred, while the second shape parameter β can be specified as the number times the event has not happened, which can also be specified as the total number of patients minus the number of patients who have

the events. [39] However, if the data presents a mean and standard error, the α and β can be specified as per Briggs et al [39]:

$$(\alpha + \beta) = \frac{\mu(1-\mu)}{\sigma^2} - 1 \quad \textbf{(1.22)}$$

$$\alpha = \mu(\alpha + \beta) \quad \textbf{(1.23)}$$

For the gamma distribution, the method of moments can be used to determine the shape parameter α and rate parameter β, and can be specified as per Briggs et al [39]:

$$\alpha = \frac{\mu^2}{\sigma^2} \quad \textbf{(1.24)}$$

$$\beta = \frac{\sigma^2}{\mu} \quad \textbf{(1.25)}$$

For the Dirichlet distribution, the approach to fitting the distribution is similar to the Beta distribution. The counts (numbers) of each type of event matching the categories of the Dirichlet are used to specify the distribution. [39] However, many software packages do not include the Dirichlet distribution as a sampling distribution. One way of generating a Dirichlet distribution is to use the normalised sum of independent gamma variables. [39] Briggs et al specified that the normalised gamma is specified as $X \sim Gamma(\alpha_j, \beta)$ [39],where $x_1, x_2, \cdots, x_k$are the draw variables with shape parameters $\alpha_1, \alpha_2, \cdots, \alpha_k$, with a common rate parameter β. Hence the required Dirichlet probabilities are then:

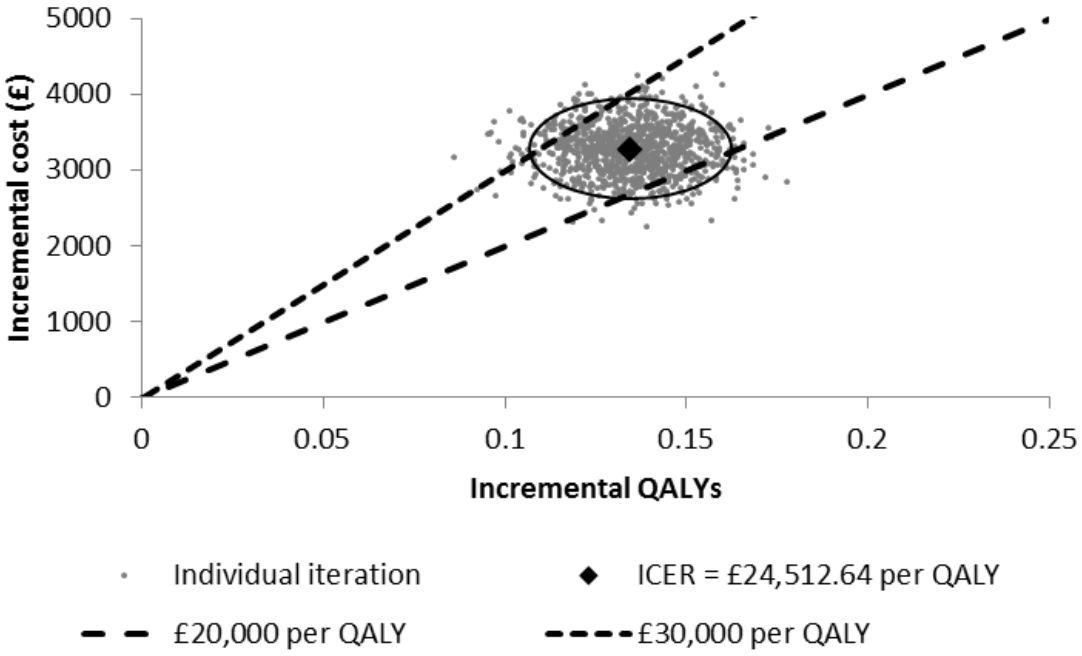
$$\pi_j = \frac{\alpha_j}{\sum_{j=1}^{k} \alpha_j} \quad \textbf{(1.26)}$$

It is this approach that will be used to fit the Dirichlet distribution in this thesis.

1.6.11 Presentation and interpretation of uncertainty

A common approach for presenting the results is to use a scatterplot of the cost-effectiveness plane. [39] This involves plotting each pairwise incremental cost and incremental benefit from each individual iteration from the Monte Carlo simulation. An example scatterplot for a hypothetical healthcare intervention is given in Figure 1.6.

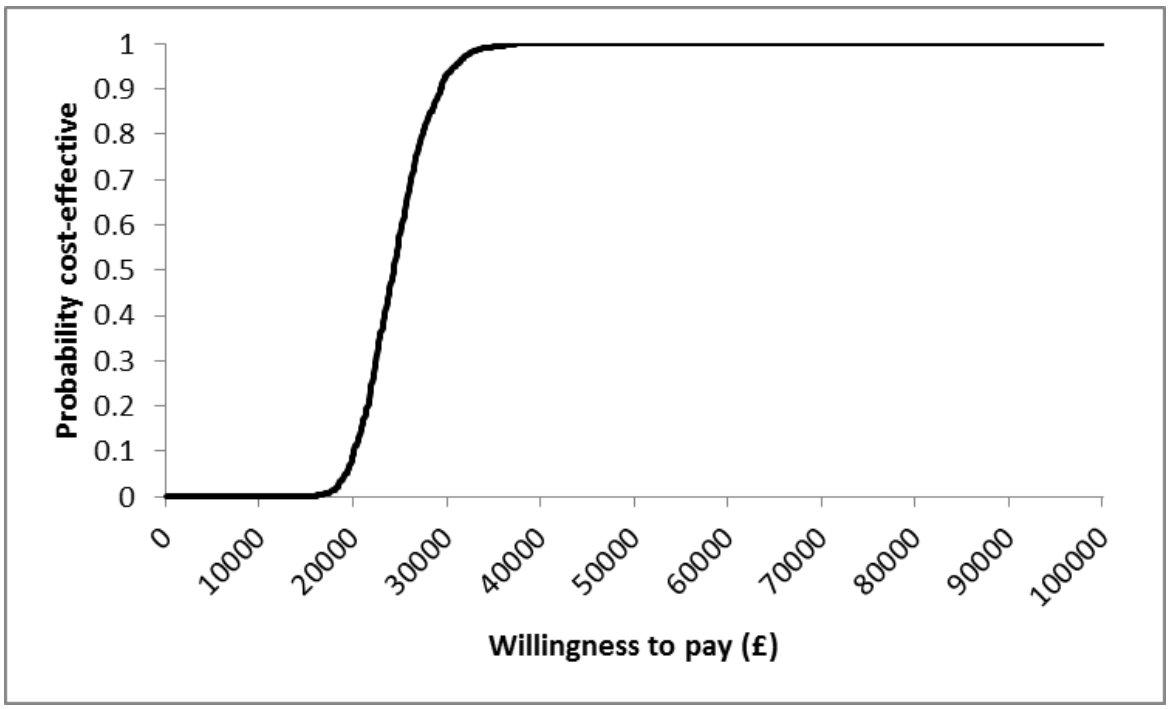
Figure 1.6: Scatterplot of incremental costs and QALYs with 95% confidence ellipse for a hypothetical intervention



The advantage of using the scatterplot is that it allows decision makers to see in which quadrants of the cost-effectiveness plane the iterations are estimated. Furthermore, as has been demonstrated in Figure 1.6, the average ICER can be plotted as well as NICE's threshold values, hence comparison can be made between the two.

However, plotting the 95% confidence interval can be problematic when the iterations pass over the vertical axis and/or horizontal axis, mainly because of the different interpretations of the ICER in the south west quadrant compared to the north east quadrant. [39] Hence, a better way of demonstrating the amount of uncertainty in the iterations is the Cost-Effectiveness Acceptability Curve (CEAC). [39, 117] This is a plot of the willingness to pay versus the probability of cost-effectiveness, which can be defined as the number of iterations which can be considered cost-effective at a particular willingness to pay. For example, a CEAC for the intervention displayed in Figure 1.6 is represented below.

Figure 1.7: CEAC for a hypothetical intervention



From Figure 1.7, it can be determined that at a willingness to pay of £20,000 per QALY, the probability that the intervention is cost-effective is approximately 9%, suggesting that only 9% of the iterations in the Monte Carlo simulation were considered cost-effective at a willingness to pay of £20,000. However, at a willingness to pay of £30,000 the probability that the intervention is cost-effective is 90%, suggesting that 90% of the iterations were considered cost-effective at that willingness to pay. Furthermore, the CEAC informs us that there are no iterations which are cost-saving, since it starts at zero. [118] If there were iterations which had cost-savings, then even if the decision maker was not willing to pay for any health benefit, there would still be a chance that the intervention was cost-effective. [118] Additionally the CEAC informs the decision maker that there is no chance that the intervention leads to no health benefit. [118] If there were any iterations in the simulation that had not lead to any health benefit for the patient, then the CEAC would not have reached one. This is because as the willingness to pay for health benefit approaches ∞, there would have been iterations where there was no health benefit, and hence would not have been deemed cost-effective. [118] It is now considered good practice to represent the results of an analysis of uncertainty using CEAC curves. [119]

1.6.12 Good practice in decision analytic modelling

There has recently been some international consensus on good practices in decision analytic modelling for economic evaluation developed in the literature, [119] This is important for this thesis as it outlines the standards to which any new improved economic model will have to conform. Some of the key areas, and details of their main standards, which are particularly relevant to this thesis are as follows:

- *Conceptualising the model:* the decision problem is clearly stated, along with the target population and health outcome used; the model structure is not defined by the data; although model simplicity is preferred, complex decision problems may require complex models. [120] For this thesis, the decision problem being answered is: are smoking cessation interventions for pregnant women cost-effective? The target population is clear; pregnant women and their infants. To define the structure of the new improved model, a critical assessment of previous evaluations will be performed to help inform the structure of the new model, as well as a review of the literature to identify relevant conditions and where their impacts may lie. Furthermore, it is likely that the new model is going to be far more complex than anything previously constructed; however whether the level of complexity is sufficient to answer the decision problem can only be discussed once the model has been described.
- *Specific requirements regarding state transition modelling:* the number of states are manageable and include all characteristics relevant to the decision problem; specifications of states and transitions should reflect the biological/theoretical understanding of the disease/condition; states should capture the type of intervention and need to be homogenous with respect to the observed and unobserved; the time horizon needs to be large enough to capture all health effects and costs; and transition probabilities should be derived for the most representative data available. [121] It is likely that this thesis will require cohort simulation when investigating the lifetime impacts of smoking on the mother [66], as well as any long-term impacts of smoking during pregnancy on the infant. These standards are important when specifying the relevant Markov models later in this thesis.
- *Parameter estimation and uncertainty:* uncertainty must be systematically explored and reported, if a parameter has little information on the uncertainty

associated with it then a conservative approach should be adopted and not the exclusion of the parameter from the uncertainty analysis; distributional forms should be continuous; both deterministic and probabilistic sensitivity analyses can be conducted; and if probabilistic sensitivity analyses are performed then CEACs should be reported. [112] In this thesis, uncertainty will be explored, although the specification of this uncertainty will be reported later in the thesis. The distribution forms will be as defined in section 1.6.10 of this thesis, and the results will be presented as recommended by the standards.

- *Model transparency and validation:* every model should have both technical and non-technical documentation outlining the model, demonstration of validation, and search from previously published analyses. [122] This thesis will provide the bulk of the technical documentation associated with the model, since it will describe how the authors critically assessed the previous literature to help aid the model structure, identified relevant conditions for the model and required parameters to populate the model, and will demonstrate the validity of the model by performing an analysis on the SNAP intervention which has been previously evaluated. [123]

1.7 A definition of strong economic evidence

Across countries, policy makers have different requirements for what constitutes strong economic evidence. These guidelines for individual health services across the world outline what is expected from economic evaluations in their respective countries. For any evaluation, it is important to know what the “gold standard” requirements are. Table 1.2 gives a brief summary of the reference cases for five countries.

Table 1.2: Summary of reference cases for economic evaluation in several countries

Country	Austria [44]	Australia [37]	Canada [38]	UK [36]	US [45]
Source of effectiveness data	Meta-analysis preferred; other sources acceptable if not available	RCT data	Systematic review	Systematic review or good quality RCT	Systematic review, however any data is acceptable if justified
Perspective of analysis	Researcher's discretion	Societal and healthcare sector	Societal and healthcare sector, ideally a lifetime horizon	Public sector perspective	Primary: payer, secondary: societal, employer
Costs	Include direct and indirect, market prices for opportunity cost (shadow prices accepted). Losses of productivity quantified using human capital method	Direct medical costs, social service costs and indirect costs. Do not include productivity costs.	All relevant costs to the study perspective; unrelated costs during a normal life year should be excluded but can be included as a sensitivity analysis	All relevant costs; any productivity/costs borne by patients and/or carers not reimbursed by the public sector are excluded	All relevant non-trivial magnitude costs, valued using opportunity cost
Outcome measurement	Researcher's discretion; must be economically or	Natural and patient related units	Should be valued in QALYs	Non-monetary outcome, preferably QALYs or DALYs	Should include both benefits and harms of alternatives

	clinically orientated. HRQoL outcomes only used where medical treatment has no prospect of cure.				
Type of analysis	Any method is acceptable using incremental analysis	Any method is acceptable; must report incremental analysis	CUA unless inappropriate, then CEA using life years gained. Must be incremental.	Any method acceptable, can be conducted alongside a good quality RCT or using modelling techniques; must report an incremental analysis	CEA must be done where possible; other methods may be used as a secondary analysis; incremental analysis should always be reported
Comparator	Standard therapy	Best clinical care/standard care	Not stated	Standard care	Standard care or best available
Discounting	5% per annum applied to costs and benefits	Costs: 5% per annum Outcomes: 0 or 5% per annum	Costs and benefits at 5% per annum.	3.5% per annum applied to costs and health outcomes	Costs at 3% per annum
Sensitivity analysis	Must include discount rate variation	One-way sensitivity analysis on all variables	One-way and two-way sensitivity analyses on	Deterministic sensitivity analysis for	Performed on 3-5 parameters and 2-3

	between 3 and 10%, otherwise researcher's discretion	using extreme values; two-way sensitivity analysis on all variables shown to be sensitive in the one-way analyses	all model inputs; must conduct a sensitivity analysis with discount rate set at 0 and 3%	key structural assumptions; PSA to explore uncertainty due to imprecision in model parameters	assumptions which have the greatest impact on the results. Discount rates varied between 0 and 7%, must include 5%

There seems to be consensus around the source of effectiveness data, with all bar Australia preferring data from systematic reviews, with good quality RCT data acceptable if no meta-analysed data is available. There also seems to be unanimity that the comparator should be standard or best available care and that the type of analysis is generally up to the researcher's discretion. However, the perspective of analysis seems to vary from the narrow view of the payer in the US to the broader societal view as found in Australia and Canada. Both Canada and the UK use HRQoL measures as outcomes, yet the US, Austria and Australia prefer outcome measures in a natural scale. The UK, Australia and Canada exclude productivity costs, which are included in Austria and the US. Discounting is applied to both costs and outcomes for all countries except the US, where it is only applied to cost. Discount rates appear to be reasonably uniform across all countries. All countries require some form of sensitivity analysis to be conducted, but only the UK requires a PSA.

A narrative review highlights a similar finding to that above. [124] Firstly, the use of CEA or CUA was preferred, expressly because the outcomes were measured in non-monetary units; a CBA was acceptable only if this information was unavailable or a suitable outcome could not be found. Secondly, the reporting of the results of the incremental analysis was considered important, and reporting average cost-effectiveness was not considered sufficient for providing evidence. Thirdly, any modelling used had to be appropriate, i.e. it had to have been designed specifically for the situation and fully justified. Finally, any time horizon used had to include all relevant consequences over the short-, and preferably the long-term. The review also highlighted that there was little agreement on areas such as the perspective of analysis, resources used and costs, and valuation of resources used. The authors suggested that the differences were caused by the varying ways that the health systems were set up across countries, specifically the dissimilarity between those that had nationalised sectors, where a more/closer to societal perspective was taken, and those where the health sector was private, which utilised a more agency perspective.

While there is considerable variation in international policy makers' requirements, recent work has been undertaken to produce a standardised reporting format for economic evaluations; the Consolidated Health Economic Evaluation Reporting Standards (CHEERS)

statement. [43] The CHEERS checklist includes 24 questions covering all aspects of reporting economic evaluations, and is reproduced in Table 1.3.

Table 1.3: The CHEERS checklist, as taken from Husereau et al (2013)[38]

Item number	Section	Item	Recommendation
1	Title and abstract	Title	Identify the study as an economic evaluation or use more specific terms such as ‘‘cost-effectiveness analysis’’, and describe the interventions compared.
2		Abstract	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.
3	Introduction	Background and objectives	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.
4	Methods	Target population and subgroups	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.
5		Setting and location	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.
6		Study perspective	Describe the perspective of the study and relate this to the costs being evaluated.
7		Comparators	Describe the interventions or strategies being compared and state why they were chosen.
8		Time horizon	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.
9		Discount rate	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate
10		Choice of health outcomes	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.
11a		Measurement of	Single study-based estimates: Describe fully the design features of the single effectiveness study

		effectiveness	and why the single study was a sufficient source of clinical effectiveness data.
11b			Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.
12		Measurement and valuation of preference based outcomes	If applicable, describe the population and methods used to elicit preferences for outcomes.
13a		Estimating resources and costs	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
13b			Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
14		Currency, price date, and conversion	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.
15		Choice of model	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.
16		Assumptions	Describe all structural or other assumptions underpinning the decision-analytical model.

17		Analytical methods	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.
18	Results	Study parameters	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended
19		Incremental costs and outcomes	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.
20a		Characterising uncertainty	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).
20b			Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.
21		Characterising heterogeneity	If applicable, report differences in costs, outcomes, or costeffectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.
22	Discussion	Study findings, limitations, generalisability, and	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current

		current knowledge	knowledge.
23	Other	Source of funding	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.
24		Conflicts of interest	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.

As expected, there are some similarities between the CHEERS statement and the international policy maker's standards, although the CHEERS statement is a broader publication checklist and as such covers areas which may not be relevant to the policy maker, such as source of funding, conflict of interest, and title and abstract. However, the topics where the CHEERS and international guidelines agree, which is relevant for this thesis, include the study perspective, choice of comparator, discounting, measurement of effectiveness, estimating resources and costs, reporting of incremental costs and outcomes, and characterising uncertainty. Furthermore, it is worth noting that regarding costs, the CHEERS statement requests that currency, price date, and conversion is reported, which is not a stated requirement of the international guidelines. This is an important consideration as the model is not reproducible where the price year is not reported, since costs would likely require inflating and this would be impossible to undertake. With regards to characterising uncertainty, although CHEERS is not explicit, it is apparent that this should be investigated through the use of PSA. However, only the NICE reference case recommends the use of this [36], which suggests that other countries' standards do not meet those of the international academic community. This thesis is aimed at both the academic community as well as the policy makers based at NICE, and hence it would therefore seem appropriate that working to the criteria as set out by the NICE reference case and the CHEERS checklist would be sensible, as well as the good modelling practices previously discussed in this chapter. [119] It is hoped that by following these guidelines, any new model of smoking cessation interventions within-pregnancy will be both useful for the academic community as well as the policy maker in the UK.

1.8 Cost-effectiveness of cessation interventions in non-pregnant populations

Smoking cessation interventions are often described as the 'gold standard' of healthcare cost-effectiveness, implying that they are cost-effective [125], and the literature is well developed and established. In 1998, Parrot et al used the previously-developed PREVENT model to estimate the health gains associated with smoking cessation in the UK. The authors combined the findings from PREVENT with the differences in the healthcare costs of current smokers and lifetime non-smokers. [126] The cost-effectiveness estimates are reproduced in Table 1.4**.**

Table 1.4: Cost-effectiveness of cessation interventions in non-pregnant smokers (from PREVENT model)

Intervention	Effectiveness	Per annum cost to UK health authority (£)	Per annum cost to UK society (£)	Discounted life years gained	Incremental cost-effectiveness per discounted life year gained (UK health authority) (£)	Incremental cost-effectiveness per discounted life year gained (UK societal) (£)
Brief advice	0.006	122,899	150,116	708	Reference†	
Brief advice and self-help materials	0.008	208,548	244,837	945	361.39	399.67
Brief advice, self-help materials, and advice to use NRT	0.009	286,437	740,285	1063	660.08	4,198.71
Brief advice, self-help materials, advice to use NRT, and specialist smoking cessation service	0.011	331,156	1,134,913	1300	188.69*	1,665.10*
†=We assume brief advice is the base intervention rather than comparing to no intervention as this would give estimates of the average cost-effectiveness rather than a incremental analysis						
*=The decrease in ICER suggests that brief advice, self-help materials, advice to use NRT, and specialist cessation service weakly dominates brief advice, self-help materials and advice to use NRT, based on the rules suggested by Karlsson et al (1996). **[127]** Hence we exclude brief advice, self-help materials and advice to use NRT, and compare that brief advice, self-help materials, advice to use NRT, and specialist cessation with brief advice and self-help materials. The new ICERs for UK health authority and societal are £345.37 and £2,507.30 respectively. From a UK health authority perspective, brief advice, self-help materials, advice to use NRT, and specialist cessation service weakly dominates brief advice and self-help materials, hence repeating the process estimates a ICER of £351.79 when comparing brief advice, self-help materials, advice to use NRT, and specialist cessation service with brief advice alone.						

The potential cost-effectiveness is clearly demonstrated; the highest ICER for the UK health authority was £345.37 per discounted life year as brief advice, self-help materials, advice to use NRT, and specialist cessation service weakly dominated all other interventions when compared to brief advice alone. However, when including costs associated with the UK societal perspective, the ICER per discounted life year was £2,507.30 for brief advice, self-help materials, advice to use NRT, and specialist cessation service. Compared with other healthcare interventions, these ICERs seem relatively low; e.g. the use of aspirin for the prevention of colorectal cancer estimated an ICER of £10,169 per life year gained. [128]

Flack et al developed a cohort simulation model for informing recent NICE guidance on cessation interventions, identifying that all, except brief advice plus self-help materials and NRT, were dominant compared to no intervention. [129] Brief advice with self-help material and NRT reported an ICER of £984 per QALY. Smoking cessation interventions are very cost-effective when compared to other aspects of healthcare, e.g. screening interventions for preventing harmful drinking in young adults have ICERs between £2,535 and £11,823 per QALY [130]; drugs for the treatment of early thrombolysis in acute myocardial infarction (MI) have ICERs between £7,219 and £10,247 per QALY [131]

Shearer et al performed a systematic review to determine the cost-effectiveness of cessation interventions in Australia. [125] Effectiveness data was obtained from international literature, while costs were estimated from the perspective of the Australian Government. The study looked at seven interventions versus an assumed background quit rate of 4%. The interventions were:

- brief advice
- telephone counselling
- NRT plus counselling
- NRT plus proactive telephone counselling
- Bupropion plus counselling

- Bupropion plus proactive telephone counselling
- Bupropion plus NRT with counselling

Quit rates ranged from 6% for brief advice to 32% for bupropion plus proactive telephone counselling. Interventions were compared with the next best alternative, e.g. telephone counselling was compared with brief advice. Only telephone counselling appeared to be dominant. Bupropion plus NRT and counselling appeared to be dominated, while the others appeared to have positive ICERs, ranging from AUD 116 (£77.11[3]) per incremental quit rate for bupropion plus proactive telephone counselling to AUD 14,340 (£9,531.80[4]) for bupropion plus NRT and counselling. The authors concluded that telephone counselling was the most cost-effective, but other interventions, such as proactive forms of telephone counselling alongside pharmacotherapies, could also be considered cost-effective. Bupropion appeared to be more cost-effective than NRT, and interventions using combined bupropion and NRT were not cost-effective.

Tengs et al demonstrated that in the US, cessation interventions were relatively cheap per life year saved, with most interventions being dominant in that they produced health gains, but saved healthcare costs overall. However, not all cessation interventions were dominant, though the most expensive was estimated to cost up to USD 13,000 (£7,727.20[5]) per life year saved for nicotine gum and cessation advice for women aged 65-69. [132] This study investigated 587 lifesaving interventions, with a median cost per life year saved of USD 42,000 (£24,964.80[6]) which includes interventions outside healthcare (e.g. environmental control). This was over three times higher than that of the most costly of the 15 smoking cessation interventions, suggesting that cessation interventions were relatively cheap in terms of average cost-effectiveness, however the authors did not report an

[3] Converted July 20th 2012, AUD 1 = £0.6647, http://www.dollars2pounds.com/AUD

[4] Converted July 20th 2012, AUD 1 = £0.6647, http://www.dollars2pounds.com/AUD

[5] Converted 2nd August 2014 USD 1 = 0.5944 http://www.dollars2pounds.com/USD/GBP

[6] Converted 2nd August 2014 USD 1 = 0.5944 http://www.dollars2pounds.com/USD/GBP

incremental analysis, therefore it cannot be determined whether the cessation interventions were cost-effective. Cromwell et al examined the cost-effectiveness of the implementation of the Agency for Health Care Policy and Research (AHCPR) smoking cessation clinical practice guidelines. [133] The study estimated that the implementation of the guideline would cost USD 6.3 billion (1995 prices) (approximately £3.7 billion[7]) in the first year, generating 1.7 million new quitters, with an average cost per quitter of USD 3,779 (£2,238.68[8]), USD 2,587 (£1,655.16[9]) per life year saved, and USD 1,915 (£1,225.22[10]) per QALY saved. Across the different interventions, cost per QALYs saved ranged from USD 1,108 to USD 4,542 (£658.60 to £2,699.76[11]), with the more intensive interventions being more cost-effective.

1.9 The necessity of separate evaluations during pregnancy

There are differences between pregnant and non-pregnant smokers which mean that within-pregnancy cessation interventions require distinctive economic evaluations. These are:

- The spontaneous quit rate amongst pregnant smokers is much higher than the general population. In the evaluation of cessation interventions for non-pregnant smokers, Flack et al used a spontaneous quit rate of 1.2% [129], while the latest statistics for smoking in England estimate that around 27% of women made a quit attempt in 2009. [134] However, estimates from the IFS 2010 suggest that in the UK, 54% of women quit smoking by the end of pregnancy. [135] This difference must be taken into consideration in evaluations of cessation interventions during pregnancy.

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[7] Converted 2nd August 2014 USD 1 = 0.5944 http://www.dollars2pounds.com/USD/GBP

[8] Converted 5th August 2014 USD 1 = 0.5924 http://www.dollars2pounds.com/USD/GBP

[9] Converted 20th July 2012, USD 1 = £0.6398, http://www.dollars2pounds.com/USD/GBP

[10] Converted 20th July 2012, USD 1 = £0.6398, http://www.dollars2pounds.com/USD/GBP

[11] Converted 2nd August 2014 USD 1 = 0.5944, http://www.dollars2pounds.com/USD/GBP

- The rate of relapse to smoking after pregnancy appears lower than in the general population. In England, around 86% of individuals who made a cessation attempt report smoking again within 12 months [134], while in California 88% had relapsed by 12 months. [136] Amongst pregnant quitters, relapse one year after pregnancy may be lower; Godfrey et al estimated that between 67% to 80% relapse by one year [4], and the 2010 IFS suggests that 31% report active smoking again by 10 months postpartum. [135]
- Cessation during pregnancy has additional health impacts not only on the mother, but her offspring as well, unlike cessation at other times where the impacts are predominantly focused on the abstaining individual. This includes both within-pregnancy as well as passive smoking impacts.

1.10 Economic evaluations of smoking cessation interventions during pregnancy

Economic evaluations of cessation interventions in the general population often exclude pregnant women, possibly because of the added complications associated with pregnancy and the impact on the infant. The current evidence suggests an economic benefit from cessation interventions during pregnancy. What follows is a brief summary of the literature; a more in-depth appraisal will be conducted in Chapter 3.

1.10.1 Systematic review of previous evaluations

A systematic review conducted in 2008 identified eight evaluations of cessation interventions during pregnancy. [6] Included studies were conducted in the US, using a mixture of CBA or CEA. The review authors noted that there was no incremental CEA or CUA, but this statement was incorrect, as several included studies reported measures of effectiveness, such as incremental cost per LBW infant avoided, and incremental cost per sudden infant death averted. Furthermore, the studies described as CBAs were in relatively cost-offset studies, since the estimated benefits came from healthcare costs averted. Four studies were conducted alongside a trial, three studies were separate modelling studies,

and one did not report what type of study it was. Two reported a societal perspective, two an agency, two were Health Maintenance Organisation (HMO), one a within-program, and one did not specify the perspective. Time horizons were end of pregnancy (three studies), first year of life for the infant (two studies), lifetime (two studies), and one study used 35 years after pregnancy. Interventions were predominantly counselling plus written materials; one was a home correspondence intervention, and three hypothetical interventions. Where the comparator was stated, it was some form of usual care (UC). Costs were either collected within the study or from established literature sources, although one study did not state the costs' source. Outcomes varied across all the studies, although no studies reported using QALYs. Outcomes included quit rates, LBW averted, pre-term births avoided, perinatal deaths avoided, neonatal intensive care (NICU) costs averted, life years gained or saved, SIDS averted, and long-term disability savings.

The results of all included studies suggested that cessation interventions during pregnancy were cost-effective. Cost benefit ratios were estimated to be between 2.1 and 3.1 for the HMO / program, 3.3:1 for NICU costs averted, and 6.6:1 for long-term disability costs averted. One study estimated that the cost savings from the intervention were between USD 365,728 and USD 968,320 (£219,656.24 to £581,572.99[12]). The highest breakeven cost for an intervention was USD 237 (£140.87[13]) per participant. The cost of preventing a LBW was USD 4,000 (£2,402.8[14]) while another study suggested that the cost per life year gained was USD 11,000 (£6,538.40[15]). The authors of the review concluded that although the literature suggested that interventions were cost-effective, there was still scope for further work, especially if some standardised methods could be adopted. The review concluded that any future evaluation should be planned alongside an RCT, with costs including NICU and maternal healthcare cost savings, and extended to a societal lifetime perspective by using QALYs discounted at three percent per annum for both the mother and the infant.

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[12] Converted 20th August 2014 USD 1 = £0.6007, http://www.dollars2pounds.com/USD/GBP

[13] Converted 2nd August 2014 USD 1 = £0.5944, http://www.dollars2pounds.com/USD/GBP

[14] Converted 20th August 2014 USD 1 =£ 0.6007, http://www.dollars2pounds.com/USD/GBP

[15] Converted 2nd August 2014 USD 1 = £0.5944, http://www.dollars2pounds.com/USD/GBP

1.10.2 A within-trial analysis of cessation during pregnancy

Ruger et al undertook a cost-effectiveness analysis using decision tree modelling of an MVI cessation intervention compared to UC. [137] The model was done alongside an RCT of low-income pregnant women in the Boston metropolitan, USA. UC was received by all participants, and consisted of a five minute presentation outlining the harmful effects of smoking during and after pregnancy, and self-help materials. MVI consisted of three home visits which educated clients about the impact of smoking on mothers, foetuses, and newborns; evaluated their smoking behaviour; helped increase self-efficacy for cessation and abstinence; and provided information on reducing exposure to environmental tobacco smoke (ETS). Each session lasted one hour. Costs of the interventions were collected as part of the clinical trial, using a micro-costing approach. The model was extended to the societal perspective, incorporating the NICU costs associated with the first year of life, and the cost savings for maternal healthcare (cardiovascular and lung disease). No difference in NICU costs was found, therefore in the base case it was assumed that the difference was USD 0, but in the sensitivity analyses the costs were varied between USD 1000 and USD 5000. All costs were reported in 1997 USD, and were updated accordingly.

The primary outcome measure for the both the trial and the evaluation was cessation and relapse prevention. Cessation was defined as a woman who had smoked at baseline (less than 28 weeks pregnant) and was abstinent at follow up (6 months postpartum). A relapse prevented was a woman who had quit smoking within three months of baseline and remained abstinent at follow up. Infant outcomes collected were birth weight and post-delivery status. Life-years saved and QALYs were calculated using published estimates from the American Cancer Society's Cancer Prevention Study (CPS II). [138] These estimates allowed for a 35% probability of relapse over the remaining lifetime, and were discounted at 3%. It was estimated that female quitters and abstainers aged 25-29 years saved 1.43 life years and 1.94 QALYs. One- and two-way sensitivity analyses were performed on the MVIs effectiveness for cessation and relapse prevention, life years gained, QALY weights, intervention cost, inclusion of maternal medical cost savings, and inclusion of cost savings for infant healthcare during the first year of life. The study performed two incremental analyses, one for smoking cessation, and one for relapse prevention.

The model estimated that the cost per participant was USD 309.20 (£206.89)[16] for MVI versus USD 4.85 (£3.25)[17] for UC. At six months postpartum follow up, MVI had a similar smoking cessation rate to UC (7/110 versus 8/100 respectively), but a much higher rate for relapse prevention (9/21 versus 5/28 respectively). The authors concluded that in the base case, MVI was dominated by UC for smoking cessation, but for relapse prevention, MVI had an ICER of USD 851 (£569.40)[18] per life-year saved and USD 628 (£420.19)[19] per QALY. In the sensitivity analyses, increasing the quit rate by 2% eliminated the domination of UC over MVI, with an ICER of USD 117,100 (£78,375.03)[20] per life-year saved and USD 86,300 (£57,760.59)[21] per QALY. Further increase in the smoking cessation rates brought the ICERs down considerably, with a 3% increase leading to an ICER of USD 19,500 (£13,053.30)[22] per life-year saved and USD 14,400 (£9,640.80)[23] per QALY. MVI remained dominated by UC under lower life-years saved, lowest QALY weights, and the inclusion of maternal and infant medical costs, with only MVI becoming cost-saving under the relapse prevention scenario. In the two-way sensitivity analyses, MVI only became cost-effective for smoking cessation with increased rates of cessation. The authors concluded that MVI was not a cost-effective intervention for cessation during pregnancy.

1.10.3 A hypothetical modelling study

Taylor adopted the Flack et al model to evaluate cessation interventions within a pregnant population for recent NICE guidance on cessation during pregnancy. [129, 139, 140] A virtual cohort of 1,000 pregnant smokers who were encouraged to quit smoking during

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[16] Converted 14th March 2013. US$1 = £0.6691 http://www.dollars2pounds.com/USD/GBP

[17] Converted 14th March 2013. US$1 = £0.6691 http://www.dollars2pounds.com/USD/GBP

[18] Converted 14th March 2013. USD 1 = £0.6691 http://www.dollars2pounds.com/USD/GBP

[19] Converted 14th March 2013. USD 1 = £0.6691 http://www.dollars2pounds.com/USD/GBP

[20] Converted 14th March 2013. USD 1 = £0.6693 http://www.dollars2pounds.com/USD/GBP

[21] Converted 14th March 2013. USD 1 = £0.6693 http://www.dollars2pounds.com/USD/GBP

[22] Converted 14th March 2013. USD 1 = £0.6694 http://www.dollars2pounds.com/USD/GBP

[23] Converted 14th March 2013. USD 1 = £0.6695 http://www.dollars2pounds.com/USD/GBP

pregnancy was modelled in six-monthly cycles over their entire lifetime using a Markov chain. The Markov chain consisted of three states; current smoker, former smoker, and dead. Interventions were those identified in the Cochrane review by Lumley et al [141], using the pooled effectiveness estimates, and an incremental CUA was performed using no intervention as the comparator. In each cycle, the model calculated the number of participants suffering from five potential morbidities:

- Lung cancer (LC)
- Coronary heart disease (CHD)
- Coronary obstructive pulmonary disease (COPD)
- Myocardial infarction (MI)
- Stroke

Outcomes were measured in QALYs, and both HRQoL and cost estimates came from established literature sources. Infants were included in the model, although no infant or pregnancy specific co-morbidities were modelled. The additional costs for infants born to mothers who smoked during pregnancy associated with the first five years of life were derived from the work by Petrou et al in the Oxford Record Linkage Study. [142] The model assumed that the relapse to smoking rate after pregnancy was 70% by 12 months postpartum, based upon expert opinion.

The model demonstrated that cessation interventions delivered during pregnancy could be considered fairly cost-effective. When compared to no intervention, the model generated ICERs of £4,005 per QALY for CBT; £3,033 per QALY for Stages of Change (SoC); £1,992 per QALY for feedback; and £2,253 per QALY for pharmacotherapies. Both rewards and 'other' interventions were dominant when compared to no intervention. The incremental net benefit statistic suggested (assuming a willingness to pay of £20,000 per QALY) that the smallest monetary benefit was £27,645,619 for SoC interventions, suggesting that society can gain £27,645,619 worth of benefit for every abstaining mother who used the SoC intervention. All other interventions reported a net benefit greater than £125,000,000.

1.10.4 Critical appraisal of the previous literature

The current literature suggests that the majority of pregnancy cessation interventions are likely to be cost-effective. However, there are relatively few economic evaluations which have attempted to demonstrate this and those models which currently exist could be improved. The systematic review by Ruger et al identified that the previous literature had no standardised approach, making it challenging to draw comparisons across cessation interventions, as well as across the healthcare sector as a whole. [6] Furthermore, Ruger at al's assessment of the quality of the literature using the standardised BMJ checklist suggested that the overall quality of previous economic evaluations was poor, which suggests there is scope for a higher quality economic evaluation. Although Ruger et al's subsequent within-trial evaluation attempted to address some of the standardised issues from the review, the evaluation still has several limitations. Although NICU costs for the first year of life were included, costs associated with long-term chronic conditions for the infant beyond the first year were not. Furthermore, only short-term chronic morbidities were included for the lifetime estimation of the mother's HRQoL and costs. Smoking has been linked with several long-term chronic conditions [143], and the Taylor model included three additional conditions. [139] This would suggest that this evaluation is missing some key costs and HRQoL impacts, which might affect the cost-effectiveness estimates of the MVI intervention.

The model constructed by Taylor was the first to undertake an evaluation of cessation interventions within the UK. [139] While this appeared to be more comprehensive than the other literature, there are still some limitations of this model. It excludes maternal specific morbidities, including ectopic pregnancy, placenta previa, and pre-eclampsia, because no data was available regarding the impact of these morbidities on the mother's utility and / or associated costs. Furthermore, no infant morbidities are included, with the impact on HRQoL coming from differences in mortality rates in the first five years of life for infants born to smoking versus non-smoking mothers. The omission of both the maternal and infant morbidities would suggest that this model is not capturing the true costs and outcomes associated with smoking during pregnancy, and that the Taylor model is underestimating the true cost-effectiveness of cessation interventions during pregnancy.

Additionally, a limitation of both the US literature and the model by Taylor is that none includes a PSA. Although one- and two-way sensitivity analyses have been included, no robust methods for capturing both structural and parameter uncertainty have been undertaken. Surprisingly, the evaluation conducted by Taylor in 2009 was conducted for the development of NICE guidance on cessation interventions within-pregnancy [140], and should thus have included a PSA, since this has been a requirement of the NICE reference case since 2004. [144] Therefore, the current literature does not inform the policy maker on the extent of decision uncertainty associated with within-pregnancy cessation interventions, and hence they have no information regarding the likelihood that the resulting decision from the evaluations is the correct one. This could be problematic because even though the deterministic result suggests the intervention offers value for money, in reality, when controlling for parameter uncertainty shows that this may only be the case 20% of the time, suggesting that 80% the cessation intervention is not cost-effective. The decision maker may feel that this is unacceptable and not wish to fund the cessation intervention; however the current literature does not allow a statement to be made regarding the probability of cost-effectiveness. Consequently, improved, more comprehensive economic models are needed to accurately demonstrate the cost-effectiveness of cessation interventions delivered during pregnancy.

Although Ruger et al utilised the BMJ checklist [6], even if the CHEERS checklist was applied to the literature [43], it can be argued that the quality of economic evaluations is poor. As has been discussed, a requirement of the CHEERS checklist is that there is a robust exploration of uncertainty, which has clearly not been undertaken. The author also argues that the current literature does not have a suitable time horizon, with only two evaluations considering longer term/lifetime impacts of smoking [137, 139], and that the cost and effectiveness estimates may be underreported because the evaluations are missing key conditions, including placenta-abruption/previa, pre-eclampsia, LBW, and SIDS. Indeed, Taylor highlighted that he excluded the within-pregnancy conditions because of a lack of data required to parameterise the model, which not only goes against good modelling practice [119], but also seems incorrect, as other previous evaluations were able to include these conditions. [65] The author concludes that not only does this suggest that there is a need for a high quality evaluation of cessation interventions within-pregnancy, but there is

also scope for a systematic review of previous evaluations using a standardised checklist which could inform the author of the key improvements required in a new high quality evaluation. Furthermore, the lack of consensus on previous evaluations suggests that, when comparing with the international gold standard for policy makers, the current literature does not meet these standards. As Ruger et al identified [6], all eight studies included in the review were conducted in the US, and as such used a narrow payer's perspective for costs and outcomes, which may meet US guidelines [45], but does not meet the guidelines for Australia, Canada and the UK, where a broader perspective is required. [36-38] Furthermore, although the US, Austria, Australia, and Canada seem satisfied with deterministic sensitivity analyses [37, 38, 44, 45], the UK requires PSAs [36]. Not one of the eight models included in the review by Ruger et al [6] meet this requirement, nor does the evaluation by Ruger et al on MVI [137], nor the model by Taylor [139]. Thus, the author argues that there is insufficient evidence for any policy maker to make a decision regarding the cost-effectiveness of cessation interventions within-pregnancy.

1.11 Should the health benefits associated with smoking in pregnancy for both mother and child be incorporated?

It is likely that any new improved economic model will include both the cost and benefits from smoking in pregnancy for both the mother and child. In previous evaluations of cessation interventions, the practice has been to sum both the QALYs associated with the mother and the infant. [139] The NICE reference case does not state whether the QALYs associated with the mother and her infant should be both included and/or combined. [36] However, the reference case does state that all direct health effects should be included, and that the time horizon should be long enough to capture all the major impacts of the intervention. [36] While it would be uncontroversial that the QALYs associated with the mother should be included in the model, since the intervention is directly impacting on her, it could be argued that the infant QALYs are irrelevant. However, as has been demonstrated, smoking in pregnancy has been shown to directly impact on foetal and infant mortality [3], as well as the chance that the infant develops asthma during their childhood. [70] This would suggest that there are direct impacts on the health of the infant and their associated QALYs, as there would be a QALY loss not only associated with premature mortality, but also from co-morbidities. Since the NICE guidance states that the

evaluation should include all relevant health benefits, it would seem logical that the infant benefits should be included in the evaluation, because they can be considered a direct health impact. However, in a model developed for the NICE guidance on in vitro fertilisation, QALYs associated with the infant were not included, since it was argued that additional lives were not improvements in health. [145] This would seem to suggest that from a NICE perspective, there may be some controversy when it comes to including infant QALYs. However, the author would argue that with smoking in pregnancy, there are improvements in health for the infant. Furthermore the model will be focused on infants that are already created, and hence they are relevant in this situation, since they are quality of life losses not only associated with morbidity but also mortality.

However, recent work by Goldhaber-Fiebert et al has demonstrated that there is considerable variation in the inclusion of QALYs associated with the infant when investigating interventions affecting fertility and childbearing. [146] The authors performed a review of the literature, looking for economic evaluations which investigated issues around fertility and childbearing, which included smoking cessation in pregnancy as well as contraception for males and females, folate supplementation, fertility treatments , and the treatment of within-pregnancy complications. The authors demonstrated that in studies where the evaluation was being performed on an intervention which had a positive outcome (e.g. smoking cessation within pregnancy, in vitro fertilisation), then generally both QALYs associated with the mother and her infant were included. However, where studies were evaluating interventions where there was no positive outcome, such as contraception and elective termination, these studies only focused on the QALYs associated with the mother/father and did not include QALYs associated with the infant. Indeed, the authors cited that such studies positively argued that the introduction of infant QALYs would bias against such interventions. [147] Goldhaber-Fiebert et al concluded that there was no consensus on whether to include or exclude QALYs associated with the infant, that current international guidance does not address this issue, and that policy makers should be focusing on doing so. [146] Furthermore, they concluded that the inclusion of infant QALYs may be biasing the results of the evaluations in favour of the intervention, and that both policy makers and researchers should reflect on this potential bias when considering the results of these types of evaluations. This statement implies that the inclusion of infant QALYs could be causing interventions to be seen as value for money,

when in reality they may not be, leading to an incorrect decision being made and the NHS/society wasting valuable resources on an intervention which should not be funded.

Although the inclusion of infant QALYs seems to be controversial [146], in this thesis infant QALYs will be included in the new improved economic model. This is because it appears to match current NICE guidance [36], as well as previous work within this topic area. [139] However, consideration will be given as to whether this may be the same result in the future, and hence the author will investigate the possibility that the model may be required to present both mother QALYs and infant QALYs separately.

1.12 Justification of thesis work

In summary, the justification for further work on cessation interventions during pregnancy can be summarised as follows:

1. There are differences between pregnant and non-pregnant smokers which justify pregnancy-specific economic evaluations.
2. There are few economic evaluations of cessation interventions during pregnancy, with only one study conducted outside the US
3. Smoking during pregnancy has been associated with several conditions that can impact on the health of a mother and her offspring, both within-pregnancy and longer term; these conditions have generally been omitted from previous evaluations. These may have been omitted due to lack of evidence or time constraints, however they are an important part of new economic evaluation
4. Generic health related quality of life measures appear underutilised in previous studies, although there is some debate as to whether QALYs associated with the infant should be included with those of the mother. However, due to previous studies including these and the lack of clear guidance from policy makers, these values will continue to be included
5. Most previous studies employ a within-pregnancy time frame, but smoking during pregnancy may have longer lasting impacts.
6. None of the previous evaluations have tackled the impact of uncertainty robustly

1.13 **Aims and objectives**

Primary aim: To develop an economic model which captures the impacts of smoking during pregnancy on the costs and health related quality of life of both the mother and her infant.

Secondary objectives:

1. To identify for inclusion in an economic model, all morbidities which are likely to have a causal association with smoking during pregnancy.
2. To systematically review and critically assess the quality of current economic literature of smoking cessation during pregnancy.
3. To use systematic review to determine accurate estimates of point prevalence abstinence from smoking at different time points after childbirth
4. To develop a model that estimates the impact of smoking during pregnancy on costs and HRQoL for the mother until the end of pregnancy
5. To develop a model that estimates the impact of smoking during pregnancy on costs and HRQoL for the infant and to directly link this to the maternal 'within-pregnancy' model (objective 4).
6. To develop a model which estimates the impact of smoking behaviour after pregnancy on health and healthcare costs of the mother for the remainder of her life
7. To construct a childhood model for the infant up to and including the age of 15 that is directly linked to the maternal smoking behaviour model after pregnancy (objective 6).
8. To combine the above four models (which will now be referred to as 'components') into an overall Economic impacts Of Smoking In Pregnancy (ESIP) model.

1.14 Structure of Thesis

This section outlines each chapter and its context within the wider thesis.

***Chapter 2**: Identification of maternal and infant outcomes related to smoking during pregnancy*

Description: Scoping reviews of the epidemiological literature to identify the conditions which have a causal association with smoking during pregnancy for the mother and infant, their incidence and their impact on the HRQoL.

Context: Identifies the most important conditions relating to smoking in pregnancy for inclusion in ESIP.

***Chapter 3:** Economic Evaluations of Smoking Cessation interventions during Pregnancy: A Systematic Review*

Description: A systematic review of the previous literature on the economic evaluation of smoking cessation interventions during pregnancy.

Context: Critically assesses the previous literature to determine the most important aspects requiring further improvement in ESIP.

***Chapter 4:** Smoking abstinence in the postpartum period after receiving a smoking cessation intervention: A systematic review*

Description: A systematic review of randomly controlled trials of the proportion of mothers abstinent from smoking for up to two years postpartum

Context: This meta-analysis generates the most accurate data currently available on the proportion of abstinence at various time points in the postpartum period used to model smoking behaviour immediately after pregnancy in the mother lifetime model.

***Chapter 5**: The ESIP model: Description of the maternal-foetal 'within-pregnancy' component*

Description: Outlines the structure and rationale for the within pregnancy components for the mother and the infant. These two models are directly linked in order to generate the impacts of smoking during pregnancy on the costs and health-related quality of life for the mother and estimate the costs and adverse pregnancy outcomes for the infant.

Context: These are the first two components of the ESIP model.

***Chapter 6**: The Mother's Lifetime Component (MLC) of ESIP: The impacts of smoking behaviour and related morbidities*

Description: Outlines the structure and rationale of the lifetime component for the mother. This models the smoking behaviour of the mother after pregnancy to estimate the impacts on costs and health-related quality of life for the rest of her lifetime.

Context: This is the third component of ESIP

***Chapter 7:** The ESIP model: Description of the childhood component*

Description: Outlines the structure and the rationale of the childhood component for the infant. This models the impact of the mother's within-pregnancy and postpartum smoking behaviour on the health related quality of life and healthcare costs of the infant up to and including the age of 15 years.

Context: This is the fourth component of ESIP

Chapter 8: *The ESIP model: How ESIP brings four components together to model the impacts of smoking and smoking cessation during pregnancy*

Description: Describes the linking of the four components into the overall ESIP model; outlines how ESIP controls for uncertainty using a probabilistic sensitivity analysis, and how ESIP was constructed using Microsoft Excel.

Context: This chapter draws together the three previous chapters into the ESIP model. It also discusses the limitations of the thesis and suggests avenues for further research.

Chapter 9: *Validity of the MWPC and IWPC*

Description: Describes a validation exercise, comparing the ESIP predictions of within-pregnancy complications and infant birth outcomes with estimates from the population statistics.

Context: Demonstrates the validity of the MWPC and IWPC.

Chapter 10: *Using ESIP to evaluate the SNAP intervention*

Description: Using data from the SNAP trial, ESIP is programmed to perform an analysis of the SNAP intervention: nicotine replacement therapy versus placebo. Both deterministic and probabilistic results are presented.

Context: Demonstrates the validity of the ESIP model as a whole for estimating the cost-effectiveness of within-pregnancy cessation interventions, and gives an example of how ESIP can be used to evaluation such interventions.

Chapter 11: *Conclusions of this thesis*

Description: A final summary of the achievements of this thesis, discussion of its limitations, their impacts, and its strengths, context in policy and scope for future improvements

Context: This draws together the thesis as a whole

Chapter 2: Identification of maternal and infant outcomes related to smoking during pregnancy

2.1 Introduction

For any economic evaluation, it is critical that morbidities included have the closest links with the intervention/disease being modelled. An evaluation could be described as misspecified if it omits important impacts on health, as it can lead to the production of misleading results, and theoretically to incorrect judgements by policy makers, with patients potentially missing out on valuable healthcare or, conversely, receiving an intervention which does not provide value for money by falling outside the established cost-effectiveness thresholds.

Although smoking during pregnancy has been linked with many harmful conditions, previous evaluations have omitted some, if not all, of these. For example, Taylor identified that smoking during pregnancy was linked with ectopic pregnancies, placenta previa, premature separation of the placenta (PROM), and pre-eclampsia. [139] However, his model failed to identify the extent to which these co-morbidities impacted on the mother's utility and/or associated costs, and therefore excluded them from the analysis. A systematic review of previous evaluations also identified this issue, with published studies only using cessation at birth as their primary outcome, generally failing to include maternal health consequences and the longer term impacts of infants' morbidities. [6] All this demonstrates that the current literature appears to be omitting important conditions; this chapter describes how the author identified the most important conditions for inclusion in ESIP.

2.2 Objectives

2.2.1 Primary Objective:

Identify the key maternal and infant morbidities that potentially warrant inclusion in an improved economic model for evaluating cessation interventions.

2.2.2 Secondary Objectives:

- To identify those maternal and infant morbidities which have any association with smoking in pregnancy
- To determine the strength of evidence for each association and hence whether there is a plausible causal link
- To identify the incidence within pregnant women of those morbidities which are considered to be causally associated with smoking in pregnancy
- Where possible, to identify QALY weights to be associated with each morbidity considered to be causally associated with smoking in pregnancy

2.3 **Methods**

2.3.1 Conditions associated with smoking and pregnancy

Objective: To identify any maternal and infant morbidity which has an association with smoking in pregnancy

It was felt that a formal systematic review was not appropriate as the main focus was to identify any condition which might be associated with smoking and pregnancy, and not to quantify the impact of smoking during pregnancy.

The review involved an electronic search of the database Medline (inception through to June 2011) for any epidemiological review articles that mentioned/discussed the relationship between smoking during pregnancy and a condition that affected the health of the mother or the infant. It was not seen as necessary to screen further databases as Medline is one of the largest medical databases, and this would have likely led to duplication without identifying further useful papers. The following search terms were used:

- Smoke
- Smoking
- Tobacco
- Pregnancy

- Pregnant Women
- Epidemiology
- Public Health
- Review

The review process involved one reviewer who screened titles and abstracts to identify relevant studies. The inclusion criteria were that studies had to be review articles (not necessarily systematic) that looked at one or more aspects of the epidemiology of smoking during pregnancy. Exclusion criteria were:

- Studies with no exclusive focus on smoking in pregnancy.
- Studies with no focus on pregnancy or infants born to smoking mothers.

The reviewer collated studies together into a table, and summarised their findings with respect to different conditions. The conditions were categorised by the individual upon whom they have a direct effect; the categories were:

- Morbidities affecting mothers only
- Morbidities affecting infants only
- Morbidities affecting both mother and infant

Since the purpose of this review was to identify any morbidity which had any association with smoking during pregnancy, the authors felt that the quality of the included articles was not informative, and therefore no quality assessment was done on included studies. There was also the consideration that no appropriate checklist could be identified as applicable to all studies (e.g. a checklist for systematic review quality would not necessarily be relevant to non-systematic reviews). Furthermore, clinical input was deemed unnecessary for this review, since any spurious associations would be excluded by the second review detailed below.

2.3.2 Summarising the strength of evidence

Objective: To determine the strength of evidence for each association

To determine the strength of evidence a further scoping review was conducted. This involved searching Medline from inception through to July 2011. Search terms included the conditions identified in the initial scoping review and:

- Smoke
- Smoking
- Tobacco
- Pregnancy
- Pregnant Women
- Newborn Infant

The following study designs were considered: case-control; cohort; RCTs; non-systematic reviews; and meta-analyses. Case-reports and qualitative studies were excluded. Studies needed to investigate whether or not there was an association between one of the conditions / morbidities identified in the first scoping review and smoking and to report either a negative or positive association (e.g. as an odds ratio or relative risk). Exclusion criteria included:

- Studies without an exclusive focus on smoking in pregnancy.
- Studies with no focus on pregnancy or infants born to smoking mothers

Citations identified were screened by title and abstract by the lead reviewer and grouped under headings relating to the conditions on which they were providing information. A second opinion from another reviewer was not sought on each study since the only data-extraction requirements were to determine the type of study and whether it supported/undermined the association identified in the previous review. The review consisted of a narrative synthesis describing the strength of evidence associated with the conditions, permitting a qualitative judgement to be made on inclusion of the conditions in the improved economic model. The qualitative weighting of studies used in decision making was based upon the hierarchy of evidence suggested by Evans et al. [148] This gives the strongest preference to systematic reviews, followed by RCTs, cohort studies, observational studies, non-randomised controlled trials, before and after studies, and case-control studies.

Consideration was also given to the criteria of strong evidence as suggested by Hill. [149] Hill defined that for a causal link to be established the evidence had to meet nine criteria:

1. Strength
2. Consistency
3. Specificity
4. Temporality
5. Biological gradient
6. Plausibility
7. Coherence
8. Experiment
9. Analogy

Not all of the Hill criteria were used, but the review focused on strength, consistency, specificity, temporality, and plausibility. Based upon these criteria, it was determined that strong evidence of a condition being linked with smoking during pregnancy was where one or more systematic reviews identified a positive association between smoking in pregnancy and an outcome. If there were no systematic reviews, but a large number (≥8) of studies supported an association, then it was judged that there was also a potentially strong association between the condition and smoking during pregnancy. This focus on either a systematic review or a large body of evidence acted as measures of the included criteria. It would be unlikely that these criteria would not be met if there was not review or meta-analysis evidence of an association, as these require existing bodies of evidence from which to determine the pooled effect. Similarly, if there were a large number of studies supporting an association, then this would seem to meet the criteria for consistency and plausibility. Furthermore, strength would also be measured due to the size of the effect linked with smoking during pregnancy, since the focus was on studies that would report significance in the size of the effect; if there was little impact of smoking in pregnancy, the size of the effect would either be small or non-existent, and most likely non-significant. Temporality would also be met, as it is likely that all included studies would be reporting results of women who had either been exposed or not exposed to smoking during pregnancy with regards to their outcomes at end of pregnancy or after pregnancy, hence looking at the incidence of the disease after the causal event. Specificity would also be met because we would be focusing in on a particular group of women; those who are pregnant.

If a condition was found to have strong evidence linking it with smoking during pregnancy, it was considered that there was a high chance that this was a causal condition, making it an important inclusion in any economic model. If there were few studies (<8), or the results of studies contradicted each other, then it was assumed there was little or no evidence for causality. Table 2.1 summarises the judgement criteria. A descriptive analysis was conducted, outlining the number and type of studies which supported a positive and negative association for the condition.

Table 2.1: Criteria and judgments on strength of evidence in review two

Criteria	Judgement	Causal link
No studies identified	No evidence for a link with smoking during pregnancy	None
A small number (<8) of studies identified, but no systematic review evidence	Weak evidence of a link with smoking during pregnancy	None
A large number (≥8) of studies, but contradictory, including contradictory systematic reviews, and/or a large number of studies identifying one link but a systematic review identifying no link	Contradictory evidence with smoking during pregnancy, therefore no association can be identified	None
A large number (≥8) of cohort and RCT studies identifying an association with smoking during pregnancy, with little or no contradictory evidence, but no systematic review	Strong evidence of an association with smoking during pregnancy	Potential causal link
A large number (≥8) of cohort and RCT studies and one or more systematic reviews identifying an association with smoking during pregnancy, with little or no contradictory evidence	Very strong evidence of an association with smoking during pregnancy	Potential causal link

2.3.3 Incidence of morbidities

Objective: To identify the incidence within pregnant women of those morbidities which are considered, from the reviews conducted above, to be causally associated with smoking in pregnancy

UK incidence data was sought, primarily from national databases/statistics considered likely to generalize all UK pregnant women. The databases identified as being the most relevant were:

- NHS Maternity Statistics for England, Hospital Episode Statistics (HES)
- Office for National Statistics (ONS)
- European Surveillance of Congenital Anomalies (EUROCAT)

However, if data on conditions were unavailable from these resources, any source of UK-specific incidence data was considered, including government documentation, and cohort studies.

2.3.4 Identifying utility weights for causally associated morbidities

Objective: To identify utility weights associated with each morbidity judged to have a causal association with smoking in pregnancy

To identify utilities associated with morbidities identified in the second review, a further Medline search was conducted, from inception till October 2013. Relevant studies were economic evaluations and/or surveys of health related quality of life using either questionnaires or preference-based measures to calculate QALYs. The search was performed for conditions that had been determined as having a potential causal link with smoking during pregnancy. However, certain conditions, such as SIDS and early and late foetal loss, required no search for utility data as a dead infant is attributed a utility value of zero. The details of the electronic search are given in Appendix 12.1. Citations were screened by title and abstract and retrieved in full if they appeared to include utility data at follow up, with details of the timing and duration of the utility loss.

2.3.5 Deciding if a condition warrants inclusion in the improved economic model

The main criterion for deciding whether a condition potentially warranted inclusion in the improved economic model was whether there was strong evidence of a causal link between smoking during pregnancy and the increased/decreased occurrence of the condition. Although the review also included incidence data regarding the conditions and utility weights, these did not influence whether the condition was potentially includable. Because the review was conducting what could be considered a comprehensive summary of the available literature, it was felt that seeking clinical opinion on whether the inclusion of the condition was correct was unnecessary because it would be highly unlikely that strong evidence of a causal association would be associated with an irrelevant condition, and hence clinical opinion would be superfluous to the decision process.

2.4 **Results**

2.4.1 Morbidities linked with smoking

Searching identified 63 citations, of which the full text of 31 articles was reviewed. This identified 32 conditions which had any association with smoking during pregnancy. The results of this can be found in Appendix 12.2. 19 conditions impacted on the mother only; 11 impacted on the infant only, and two impacted on both mother and infant.

2.4.2 Strength of evidence

The second search identified 4,323 citations. Some conditions retrieved many citations, e.g. LBW (689 citations), whilst others had very few e.g. placenta accreta (two citations). All studies were screened by title and abstract; 766 citations were judged relevant. It was beyond study resources to perform a full text review, so judgements were made on the basis of information included in study abstracts. Where an abstract was unclear, the full text was retrieved (41 studies). If a study appeared to be a systematic review, full text was again retrieved (39 citations). Further details of cited articles can be found in Appendix 12.2; a brief summary of this large literature follows.

2.4.3 Outcomes / morbidities for which no evidence was identified:

No studies were identified supporting any association between smoking during pregnancy and pregnancy bleeding of unknown origin, stroke, pulmonary embolism, MI, influenza, bronchitis, gastro intestinal ulcers, or uterine fibroids. There was judged to be no evidence linking these conditions with smoking during pregnancy, despite articles identified in the initial review claiming otherwise.

2.4.4 Outcomes / morbidities for which limited evidence was identified:

A small number of studies were identified supporting an association between smoking in pregnancy and pregnancy accreta (one case control), pregnancy rhinitis (one survey), deep vein thrombosis (two case control), asthma (two case control and one cohort), vomiting during pregnancy (one cohort and one survey), and lower quality of life for the infant (one cohort). Therefore, for these conditions, the judgement was that there is insufficient evidence to support the notion of a causal association between these morbidities and smoking during pregnancy.

There was contradictory evidence for gestational diabetes and childhood cancers. For gestational diabetes, only three studies identified reported an association with smoking in pregnancy (one cohort, one cross-sectional and one RCT), while two systematic reviews and two cohort studies found no association. The judgement was made that there was no association between smoking during pregnancy and gestational diabetes in the mother. For childhood cancers, six case-control studies reported an association with increased risk of cancer due to smoking during pregnancy. However, two non-systematic reviews and 13 case-control studies reported no association. Consequently, the evidence linking smoking during pregnancy and childhood cancers did not meet our criteria for being ‘strong’.

Limited and unclear evidence was also identified for otitis media (two observational studies reporting an association and one not); infants’ subsequent fertility (two cohorts and one RCT reported no association, one cohort reported an association) and obesity in infants (two reviews, six cohorts, and eight observational studies reported some association while one review reported no association). One case control and two cohort studies attributed an association with impaired cognitive development in infants and smoking during pregnancy,

while six cohort studies identified no such association. Since none of the identified studies include a systematic review, and the evidence seemed contradictory, the judgement was made that there was no evidence for an association between these conditions and smoking during pregnancy.

An increased risk of behavioural problems in childhood was linked with smoking during pregnancy in 67 studies (seven review, 15 cross sectional, nine case control, 19 cohort, and 16 longitudinal), while only 13 (four review, two cross sectional, two case control, two cohort, and three longitudinal) suggested there was no association. However, one systematic review was identified, which estimated that there was no association. Although the majority of studies seemed to identify a positive association with smoking during pregnancy, the evidence appears highly contradictory, especially since the systematic review found no association. Thus, even though there are many studies investigating the link between smoking during pregnancy and behavioural problems, the evidence is far from conclusive.

2.4.5 Outcomes/ morbidities where strong evidence was identified:

For maternal conditions, strong evidence supporting a potentially-causal association was identified for placenta previa (one systematic review, six case control, and five cohort studies), placental abruption (two systematic reviews, 11 cohort and six case control studies), PPROM (one systematic review and seven case control), and ectopic pregnancy (one systematic review, one review, eight case control, and one cross sectional). For pre-eclampsia, 26 studies (including three systematic reviews) reported a negative (i.e. protective) association with smoking in pregnancy, while five cohort studies found no association or an increased risk. Since the evidence was stronger for the protective impact, the judgment was made that there was strong evidence supporting that association, and hence smoking had some protective effect.

For materno-foetal conditions, the majority of evidence implied there was an association between smoking during pregnancy and both pre-term birth and early and late foetal loss. For foetal loss, one systematic review, 30 cohort, 11 case control and 12 reviews suggested there was an increased risk from smoking during pregnancy, while five cohorts and two case controls identified no association; therefore, it was judged that there was strong

evidence of a detrimental association and a potentially-causal link. For premature birth, no systematic reviews were identified; however, 28 cohort and 12 case control articles all supported a positive association, while five cohorts and two case controls supported no association. With such a large number of studies supporting a positive association with an increase in premature births amongst smokers, it was decided that there was strong evidence of an increased risk of preterm birth from smoking during pregnancy.

For infant conditions, strong evidence was found for an association with SIDS. Strong but contradictory evidence was also found for LBW, behavioural problems, congenital anomalies, and respiratory illness. For LBW, there was strong evidence linking smoking during pregnancy with a reduction in birth weight, with one systematic review, six reviews, one cross sectional, 36 case control, and 117 cohort studies supporting this association. However 11 studies (six cohort, four case control, and one cross sectional study) suggested there was no association. For respiratory illness, one systematic review, 44 cohort, nine reviews, seven case control and two cross sectional studies suggested there was a link between smoking during pregnancy and an increased risk of respiratory illness in the infant, while only three cohort studies suggested there was no association. For congenital anomalies, an increased risk due to smoking during pregnancy was identified in two systematic reviews, six cohort, nine case control, and two review studies. Seven cohort and two case control studies identified no association. It was judged that since the vast majority of evidence, often with higher quality study designs, favoured positive associations, there was strong evidence of a potentially-causal association with smoking during pregnancy for these outcomes.

2.4.6 Incidence of outcomes for which strong evidence was identified

For all the conditions identified as having strong evidence associated with smoking during pregnancy, a further search of national statistics was undertaken to determine the annual frequency of occurrences in the UK population as a whole. The incidence for each condition is reported in Table 2.2, Table 2.3, and Table 2.4.

Table 2.2: Incidence of conditions that impact on the mother only

Morbidity	Incidence
Placenta previa	Occurs in 0.66% of deliveries [150]
Placental abruption	Occurs in 0.4% of deliveries [150]
Pre-term premature rupture of the membranes	Occurs in 9.64% of deliveries [150]
Ectopic pregnancy	Rate of 1.7 per 100 deliveries [150]
Pre-eclampsia	Occurs in 1.97% of deliveries [150]

Table 2.3: Incidence of conditions that impact on both the mother and infant

Morbidity	Incidence
Pre-term birth	Occurs in 5.69% of deliveries [150]
Early and late foetal loss	Rate of 4.9 Stillbirths per 1,000 total births [151] Miscarriage occurs at a rate of 5.9 per 100 deliveries [150]

Table 2.4: Incidence of conditions that impact on the infant

Morbidity	Incidence
SIDS	Rate of 0.2 per 1,000 live births [152] For a child born less than 2500 grams (LBW), rate is 0.5 per 1,000 live births, and 0.2 per 1,000 live births over 2500 grams [153]
LBW	Rate of 70 births per 1,000 live births [153]
Congenital anomalies	Rate of 179.43 for all congenital anomalies (excluding chromosomal) per 10,000 births [154]
Respiratory illness	21% of children have a diagnosis of asthma. 19% of children report wheezing [155]

2.4.7 Identification of utility weights associated with morbidities for which strong evidence was identified

A search was performed to identify relevant utilities associated with includable conditions which could be used within an economic model. This returned 942 citations covering all conditions except placental abruption. From the 942 citations, 11 studies were identified as reporting relevant utility data; no relevant studies were identified for placenta previa, placental abruption, and PPROM. Table 2.5, Table 2.6, and Table 2.7 summarise the evidence found.

Table 2.5: HRQoL weights attributable to morbidities impacting on the mother only

Morbidity	Utility weights identified
Ectopic pregnancy	A 0.01 utility decrement for a mother who suffered from an ectopic pregnancy, which was applied for one cycle only. [156]
Pre-eclampsia	One study identified that was a lack of data regarding utilities for pre-eclampsia and therefore consulted the clinical guideline development group who had commissioned the model. This group of experts recommended that there was no impact on utility. [157]

Table 2.6: HRQoL weights attributable to morbidities that impact on both the mother and the infant

Morbidity	Utility weights identified
Pre-term birth	See LBW
LBW	In children born with very LBW (below 1501 grams), up to age five, the utility weights were 0.915 for those born at 23 weeks gestation, 0.950 for those born 24-25 weeks, 0.960 for those born 26-27 weeks and 28-29 weeks, and 0.970 for those born at 30-31 and >31 weeks. [158] Extremely LBW infants (below 1000 grams) between the ages of zero and five were awarded utility weights between 0.7 to 0.9 for mild disability, 0.4 to, 0.8 for moderate disability, and 0.1 to 0.7 for severe disability. [159]

Table 2.7: HRQoL weights attributable to morbidities impacting on the infant only

Morbidity	Utility weights identified
Congenital anomalies	Children born with Spina Bifida: average utility 0.55. [160] Children born with undiagnosed craniosynostosis have a utility of 0.95 and a standard error of 0.24. [161, 162]
Respiratory illness	Estimated average utility for mild intermittent asthma was 0.91 (standard deviation (s.d.) of 0.18), mild persistent asthma was 0.90 (s.d. of 0.18), and severe persistent asthma was 0.83 (s.d. of 0.21) in children under the age of 18. [163] Utilities for elementary school aged children with asthma estimated (range) as 1.0 (0.98 to 1.0) for a symptom free day, 0.9 (0.84 to 0.96) for symptomatic, 0.70 (0.64 to 0.76) for recovering from attack, 0.43 (0.37 to 0.49) for an attack that required a visit to an emergency department, and 0.06 (0.01 to 0.11) for an attack which required hospitalisation. [164] Utility loss for an episode of wheezing 0.0018 (0.0003 to 0.005) among children aged less than five years. [165] Asthmatic patients aged 12-19 years had a utility of 0.90 (s.d. of 0.12). [166]

Whilst reviewing the papers, it became apparent that there was some evidence of an impact of losing the child on the health of the mother. Partridge et al incorporated this impact by awarding women who had lost their child during pregnancy with a utility of 0.9. [167]

2.5 Discussion

This chapter demonstrates how widespread the impact of smoking during pregnancy is; systematic searches have summarised the strength of the evidence associated with morbidities likely to be caused by smoking in pregnancy. There is evidence for a causal relationship between this and 11 major morbidities. Furthermore, utilities for maternal conditions appear to be relatively sparse.

2.5.1 Strengths of the reviews

The Hill criteria were utilised in our judgement of whether there is a causal relationship between smoking and several conditions which have an impact on the health of the mother and/or her infant. [149] These criteria have been widely accepted as guidelines for drawing causal inferences for nearly fifty years. [168] However, the Hill criteria have been criticised in recent years. Philips et al argued that the basic mechanism of determining causality is in scientific common sense deduction rather than through the use of predetermined specific criteria. [169] Other researchers argue that the study design may rule out deducing causality, and that the Hill criteria are only of use for inferring the best explanation of the data. [170] However, it has been argued that the criteria still apply, but rather than using them to prove causality, the counterfactual approach should be adopted for each criterion to try and disprove causality. [171] Howick et al argued that the Hill criteria were still useful for determining causation, but that they should be organised into three categories; direct evidence from studies (probabilistic association between intervention and outcome is causal and not spurious), mechanistic evidence (of the alleged causal process), and parallel evidence (other evidence of the hypothesis). [172] Howick et al suggested that the revised form of the Hill criteria put more emphasis on direct evidence of the association and its effect size, which appears to be particularly relevant to the approach the author has used in applying the criteria in this chapter. All this suggests that even though the Hill criteria are debated in the current literature, their application is still judged to be a relevant method for investigating causality.

Our judgement may not have used all of the criteria suggested by Hill [149]; however, our definition of a causal relationship does meet several. Most importantly the judgement meets the criterion of consistency, since we defined strong evidence as one or more systematic reviews, and/or a large number of studies with reasonably strong research design consistently indicating associations. It also meets specificity, as we are dealing with a generally homogenous population, pregnant women; temporality, since the conditions are observed either during, or at the end of pregnancy; while the mother has either been smoking before pregnancy and quit upon conception / in early pregnancy or has smoked throughout gestation. Finally we also meet plausibility; since we already know that in the general adult, non-pregnant population smoking has many diverse impacts it would seem likely that smoking during pregnancy can plausibly have impacts on those conditions

identified. Although not reported, the strength of the effect is also touched on with this review. The actual strength of the impact of smoking is not that important, however, since we stated that the CI did not cross one (i.e. no association), we have already constrained our review to focus on those conditions where there is a statistically significant effect, meeting the first of the Hill criteria. We have not investigated whether the current literature meets the requirements of biological gradient, coherence, experiment, and analogy; by not meeting these criteria we may be incorrect in assuming that there is a causal relationship. However, while we have not investigated biological gradient specifically, included studies may report this information, although it is not summarised in this review. We decided not to focus on biological gradient because we were interested in the impact of smoking versus not smoking rather than smoking exposure, since we are investigating cessation interventions aimed at stopping smoking and not reducing smoking. If we were focusing on interventions to reduce smoking, then the biological gradient aspect would have been important as we would require evidence of the impact in the reduction of smoking from a heavy smoker to a light smoker. We did not include coherence and experiment because we were interested in epidemiological evidence in pregnant populations rather than the results of laboratory studies; Hill himself cannot nullify evidence of an effect from epidemiological studies. [149] Finally we did not include analogy because we were only interested in the impact of smoking during pregnancy on the risk of the diseases occurring, and not whether any other factors may have a similar impact as they could be considered exogenous from our model. However, it is hoped that by focusing primarily on systematic review and meta-analysis evidence, these will have controlled for any similar factors which may have had a confounding effect on the impact of smoking in pregnancy. This would mean that our criteria for strong evidence, and hence a causal relationship, meets five of the nine criteria, suggesting that we are likely to be correct when suggesting a potential causal relationship between smoking and the 11 conditions.

This work is not a standard systematic review. To meet the objective of critically assessing the evidence for 32 conditions linked with smoking during pregnancy, 32 systematic reviews would have been required, which is beyond the scope of this thesis. However, this review does employ elements such as a systematic search, which means it is likely to be sufficiently robust for identifying potentially relevant morbidities for economic evaluations of cessation during pregnancy. The review appraised approximately 4,000 citations, giving a comprehensive overview of morbidities linked with smoking during pregnancy. It is also

likely that correct judgements are being made, as only those with a large number of studies suggesting a consistent association are deemed to have a causal link with smoking during pregnancy.

2.5.2 Limitations of the reviews

There are several limitations of this review. Although a systematic search strategy was used, we did not formally assess the quality of the included studies, making it impossible to determine whether the findings are based upon high quality studies. In an attempt to counteract the potential bias this may cause, the authors defined strong evidence as the existence of one or more systematic reviews supporting a particular association. Systematic reviews are seen as the gold standard in the hierarchy of evidence, and often incorporate quality assessment as part of their reviewing process. In all but one of the outcomes the authors judged there was strong evidence to support an association from at least one systematic review. In the case of premature birth, where no systematic review was identified, there were a very large number of studies supporting the association, so our assumption of strong evidence would appear justified.

A second limitation was that the electronic searching was limited to one database. We could, therefore, have failed to identify important studies that might be contradictory to findings. However, Medline is an established database with a broad remit, so it would be unlikely that unsearched databases would add substantially to the evidence found. Further searching could have led to the inclusion of more poor quality studies which may have increased the difficulty of making judgements on the strength of evidence.

Another limitation was that we were unable to determine the impact of publication bias. As part of a meta-analysis, funnel plots can investigate this, but as our synthesis of data was qualitative no funnel plot was available; thus there could be unpublished studies which we did not find and which contradict our conclusions. In the case where the decision was made without evidence from systematic reviews, there was such a difference in number of studies supporting the association compared to the number of studies not supporting it that it is unlikely that the wrong decision has been made.

2.5.3 Implications for the proposed model

These reviews highlight a total of 11 conditions that have some causal relationship with smoking in pregnancy and potentially warrant inclusion in the improved economic model. The predominant impact of smoking during pregnancy appears to be negative on the health of the mother and the infant; however, there does appear to be some protective effect on pre-eclampsia in the mother. It is important that the economic model includes both negative and positive health impacts; this is because there may be important cost and HRQoL implications which could be important determinants of the cost-effectiveness of interventions being evaluated. The omission of these conditions could suggest that the previous literature has been misspecified and therefore the improved economic model should attempt to include most, if not all, of the causally associated diseases.

The first review highlighted 18 pregnancy-specific maternal conditions, 14 of which had negative impacts on the health of the mother. However, only six conditions appeared to have a causal association. Although we have no way of assessing publication bias, the review could highlight some publication bias existing in the conditions where we found no evidence, or contradictory evidence, i.e. in that small studies criticizing the association have not been published. However, the second scoping review might garner the possibility that the authors of the epidemiological reviews from the first review were mistaken in their judgments of these conditions.

The incidence of the six maternal conditions linked with smoking in pregnancy is relatively low. Furthermore, we have no evidence to support any HRQoL impact, both within-pregnancy and longer term. The literature reviewed would suggest that any HRQoL impact is relatively short-lived, which might explain why there seems to be little evidence of a change. It could be reasonably argued that these conditions do not warrant inclusion in any economic model; however it is likely that there are substantial related healthcare costs, especially since all require some form of emergency care, which, along with the strong evidence of a causal association, imply that these maternal conditions should be included in any economic model, despite the infrequency and lack of HRQoL impact.

The review has also highlighted that there is strong evidence of a causal association between smoking and foetal loss during pregnancy and within one year of birth. This

includes conditions like ectopic pregnancy, miscarriage, stillbirth and SIDS and implies that there are preventable deaths occurring. This is significant because there is potentially a tremendous gain from preventing these deaths. Furthermore, we found evidence to suggest that foetal loss has a detrimental impact on the mother. Miscarriage and foetal loss have been associated with postnatal depression which can last up to 12 months after the miscarriage and beyond. [173, 174] This is an important consideration since smoking during pregnancy increases the chances of foetal loss both during pregnancy and after birth. The impact was incorporated into an economic evaluation by awarding a utility of 0.9 (rather than 1) to women who lost their child during pregnancy. [167] The model used by Partridge et al used this weight for 50 years, the remaining life expectancy; however it could be argued that this depressive state is a more transient condition, since little evidence of long-term impacts appear to exist. The persistence of any effect is important; for example, a short term impact lasting for no more than one year might not be influential in economic terms but longer term impacts are potentially worth considering.

There was also strong causal evidence of an association with several birth outcomes for the infant, such as premature birth and LBW. However, these two conditions seem to be very closely linked and this was reflected in some of the estimates of HRQoL impacts. The PERFECT study demonstrated this clearly with the greatest losses in QALYs associated with infants by age five which had been born with very LBW and prematurely. [158] In a separate study of a Finnish cohort, the authors demonstrated, using a multiple regression analysis, that length of gestation had a bigger impact on the quality of life than birth weight, with a utility increase of 0.28 (95% CI 0.21 to 0.36) per one extra week gestation from 23 weeks and longer, while a 100 gram increase in weight increased utility by 0.007 (95% CI -0.04 to 0.06). [175] The link between birth weight and prematurity is logical, since the shorter the gestational period, the higher the chance the foetus has not developed fully, and therefore the more likely the foetus will be born with LBW.

The HRQoL impacts on infants for LBW and premature birth would appear to be small, and dependent on other factors. As mentioned, the PERFECT study attributed the lowest utility of 0.915 to infants born at 23 weeks and with very LBW. [158] This suggests a utility loss of 0.085 per year period up to the age of five. However, only 0.1% of live births in England and Wales in 2011 occurred at less than 24 weeks gestation, with a mortality rate of 89%, and most deaths occurring within the first week of life. [176] The majority (81%) of pre-term

infants are born between 32 and 36 weeks gestation [176], where the PERFECT study estimated that children aged five or less had an estimated utility of 0.97, a loss of 0.03. [158] In the other studies identified, LBW and/or premature birth were not associated with any loss in quality of life per se, rather this was dependent on whether or not a LBW infant developed a disability. This was the case in Doyle et al, where the utility was determined by the degree of disability the child was assumed to have. [159] It has been estimated that around 62% of infants born at 27 weeks gestation or before have some form of disability, with around 51% being oxygen dependent at home or in hospital, and 17% having some form of brain injury. [177] With such serious disabilities, which can have severe long-term impacts, it is easy to understand why the utilities should be assigned dependent on whether the child has a disability or not. However, 2011 ONS data for England and Wales estimated that 0.4% of live births were LBW and 27 weeks gestation or less; of these infants, 83% were dead within one year of birth. [176] Although the literature suggests that an infant born prematurely and/or LBW can suffer a severe utility loss due to a disability, the occurrence seems so infrequent as to not warrant inclusion in the model. Furthermore, additional research would be required to determine the nature and strength of relationships for the disabilities and LBW/premature birth, which is beyond the scope of this thesis.

Smoking during pregnancy had potentially-causal relationships with only two infant conditions. For the other seven conditions, evidence was contradictory; this may be due to the studies not being powerful enough to identify an association or that indeed no such association exists. The most important finding of these reviews was that there was no positive impact of smoking during pregnancy on the health of the child; all nine conditions had detrimental effects. These impacts seem to be important in both the short- and long-term. The two causally- associated conditions, congenital anomalies and respiratory illness, can both have lasting and significant impacts on the health of the child. A congenital anomaly in pregnancy could either be a minor disability or alternatively could be very severe; however, they are among the most infrequent conditions linked with smoking in pregnancy. Respiratory illness, on the other hand, is one of the most prevalent chronic diseases that can occur in childhood. In a worst case scenario, respiratory illness can lead to a severe HRQoL loss for the child. However, more frequently there appears to be a relatively minor impact on health. These reviews highlight that a vital component of evaluations of smoking in pregnancy are the health impacts on the infant.

One important consideration for ESIP is that adopting this process of identifying morbidities with causal associations has resulted in a lower risk of misspecification. From the initial review, all 32 conditions could have been considered worthy of inclusion; however, it has been demonstrated that 21 of these conditions have no evidence of a causal association, and therefore appear to have no justification for inclusion. For example, Godfrey et al included otitis media in their costing analysis of smoking during pregnancy. [4] This review did not find any evidence of a causal association between smoking during pregnancy and otitis media, and therefore the inclusion could be considered a misspecification error. ESIP has avoided this potential error, and thus could be deemed more robust.

2.6 **Summary**

In conclusion, smoking during pregnancy has been linked with many conditions, both impacting on the health of the mother and the health of her offspring. However, only 11 conditions have strong evidence suggesting that smoking during pregnancy causes them, and hence warrant consideration for inclusion in the improved economic model. Utility for the mother does not seem to be impacted by several of the pregnancy specific maternal morbidities. For LBW and premature birth, HRQoL seems to be most reduced in the presence of both conditions; however, the occurrence of LBW or premature birth does not seem to have any lasting impact on the utility of the infant unless the child develops a disability, which appears to be relatively infrequent. This has several important implications for the development of an improved economic model:

1) Pregnancy specific maternal conditions which are likely to be caused by smoking (pre-eclampsia, placenta previa, placental abruption, and ectopic pregnancy) occur infrequently and have little sustained impact on maternal HRQoL.
2) Infants born prematurely and/or with LBW experience no long-term impacts on health from these conditions. These conditions seem to be closely linked and therefore the discrete impacts on HRQoL from one or other condition are very hard to ascertain.
3) The majority impact on HRQoL of LBW or premature infants is determined by whether or not they are born with a disability, or develop one in childhood.

4) Congenital anomalies have a large impact on infants' HRQoL; however, they occur infrequently.
5) Respiratory illnesses have a relatively high incidence and a large, long-term impact on the infant's HRQoL.

Chapter 3: Economic Evaluations of Smoking Cessation interventions during Pregnancy: A Systematic Review

3.1 Introduction

As Chapter 1 demonstrates, there are relatively few evaluations of smoking cessation during pregnancy. For the proposed model to be robust, it is important to critically assess the previous literature to identify any weaknesses or omissions. Ruger et al attempted to do this in 2008 with a systematic review [6], however this could now be considered outdated; therefore it would seem pertinent to update it for the purpose of this thesis. This updated review would help focus the author on the areas with significant issues or oversights in order for the proposed economic model to be considered an improvement on the previous literature.

3.2 Review aims and objectives

3.2.1 Primary objective

To identify and critically assess economic evaluations of smoking cessation interventions in pregnant women.

3.2.2 Secondary objectives

For included evaluations, to identify the:

1) extent to which impacts of smoking on the mother are considered, including both smoking specific morbidities and associated pregnancy specific outcomes
2) extent to which impacts of smoking on infants are considered
3) length of time horizon and follow up period of the economic evaluations
4) extent to which relapse to smoking after childbirth is considered by the economic evaluations
5) specific modelling techniques that have been employed and critically assess them
6) areas where the methodologies of the evaluations require further development

7) identify if there are any suitable decision analytic model structures which may influence the design of the new improved economic model

3.3 **Methodology**

3.3.1 Database selection

11 databases were searched: ASSIA, CINAHL, Econlit, Embase, Maternity and Infant Care, Medline, NHS EED, PsycArticles, PsycINFO, PubMed and Tufts Cost-Effectiveness Analysis Registry.

To capture evaluations conducted for government policy purposes (or similar studies) in the 'grey literature' (studies published outside peer reviewed journals), two broad databases, Web of Knowledge and Web of Science were searched. These databases incorporate an array of 'grey literature' sources, including conference proceedings, governmental and business reports and theses. Additionally, the websites of NICE in the UK and the US Surgeon General were searched to identify any evaluations conducted as part of public health or health technology guidance. [178, 179]

An initial search was conducted on all databases from inception through to July 2011; this was later updated up to August 2014 during thesis writing up.

3.3.2 Search terms

The search strategy was developed using terms from a previous review and the Cochrane Pregnancy and Childbirth Group. [6, 180] Search terms were:

- smoking
- smoking cessation
- relapse
- relapse prevention
- tobacco
- pregnant women

- pregnancy
- antenatal
- prenatal
- Pregnan*
- Fetus
- Foetus
- Fetal
- Foetal
- Newborn
- cost
- cost analysis
- cost effectiveness
- cost-effectiveness
- cost benefit
- cost utility
- economic evaluation
- economic
- QALY
- quality adjusted life year*
- quality-adjusted
- quality of life
- cost per life year;

For the search of the NICE and US Surgeon General websites, the terms smoking, smoking cessation, and pregnancy were used.

3.3.3 Inclusion criteria

Studies were included if they were in English, reported an original, formal economic evaluation, with a direct comparison between costs and outcomes, e.g. 'cost per quitter'. Studies not published in English were not included because it was felt that the translation process would not be adequate and could lead to misinterpretation of the model.

Population: Women who had experienced a cessation intervention during pregnancy and/or their offspring, or hypothetical cohorts modelling cessation during pregnancy and/or after this.
Interventions: Any interventions or combination of interventions, both real and hypothetical, aimed at encouraging pregnant smoking women to quit.

Comparators: No intervention or 'usual care' (UC)

Outcomes: Clinical or economic outcomes considered relevant to the mother and/or child (e.g. smoking status at end of pregnancy, LBW averted, SIDS averted, and QALYs).

Design: Any study design could be included. The following economic evaluations would be considered:

- cost-benefit analysis (CBA); outcomes in monetary units compared to costs
- cost-effectiveness analysis (CEA); outcomes in natural scale (e.g. length of stay in hospital) compared to costs
- cost-utility analysis (CUA); where outcomes on a generic scale (e.g. QALYs) compared to costs

3.3.4 Exclusion criteria

Exclusion criteria were:

- Studies with no economic analyses.
- Studies which did not include an outcome relevant to both smoking and pregnancy.

3.3.5 Identification of papers

Citations were screened by title and abstract by the lead reviewer and potentially-relevant texts were retrieved. If a protocol for an ongoing RCT was identified, the principal investigator was asked to provide any available analysis. Two reviewers working independently assessed full texts for inclusion, extracted data, and applied a quality assessment checklist (see Section 3.3.7). If the two reviewers disagreed on the data

extraction or quality assessment, a third reviewer was consulted. A manual search was conducted of references to identify other potentially-relevant studies, which were then identically screened and reviewed.

3.3.6 Data extraction

Data extracted included:

- setting (real data versus hypothetical modelling)
- description of intervention
- description of comparator
- outcomes measured
- characteristics of resource estimates
- characteristics of cost estimates
- study assumptions
- modelling assumptions
- discounting
- sensitivity analysis performed
- type of economic evaluation
- results of economic evaluation
- comparison with other economic evaluations

The following characteristics were noted:

- author(s)
- years of study
- publication year
- study type and design
- topic and study question
- funding source

3.3.7 Quality assessment

To assess methodology quality, a suitable assessment checklist needed identifying. A brief scoping review of Medline was conducted in March 2011 to identify relevant economic evaluation checklists. However, since this search was conducted, the CHEERS statement has been produced and is now the accepted gold standard for the quality of economic evaluation studies. [43] Since this review was conducted in the autumn of 2011 and updated in August 2014, the results of the review which informed the construction of the improved economic model were based on the QHES assessment, therefore it was decided to continue to utilise the QHES rather than adopting the CHEERS statement. The scoping review search identified these health economic quality checklists:

- British Medical Journal Checklist (BMJ) [181]: Comprises 35 'yes/no/not clear/not applicable' response questions covering three topic areas: study design, data collection, and analysis and interpretation of results.
- Consensus Health Economic Criteria (CHEC) [182]: Consists of 19 'yes/no' response questions focusing on the methodological quality of economic evaluations.
- Quality of Health Economic Studies (QHES) [183]: Contains 16 'yes/no' response questions focusing on the both the methodology of economic evaluations and the broader study, with each question carrying a weighted point score out of a total of 100.
- Assessing Quality in Decision Analytic Cost-Effectiveness Models [184]: Focuses on nine dimensions of quality, each with a subset of 'yes/no' response questions.
- Reporting Format for Economic Evaluations [185]: Covers 13 major dimensions with 'yes/no' response questions.

Checklists developed by Sculpher [184] and Nuijten et al. [185] were identified but rejected because they focused on advanced modelling techniques and virtually no previous studies had used such methods. [6] The BMJ, CHEC, and QHES checklists are similar in that they are all subjective measures which incorporate descriptive components. However, unlike the BMJ and CHEC checklists, the QHES had a quantitative aspect, with each question carrying a weighted point score, out of a maximum of 100, which could allow interpretation of the overall quality of study, and a direct comparison with other studies in the same topic area. Furthermore, the QHES has been demonstrated to have good internal

validity [186-188], produces similar results to other quality checklists [187], and covers the same topics as other checklists but is very easy in its application. [188] These were identified as the advantages for using the QHES checklist, and hence the QHES was adopted as the method of quality assessment for the review. The QHES instrument can be seen in Table 3.1.

Table 3.1: The QHES instrument

	Questions	Points	Yes	No
1	Was the study objective presented in a clear, specific, and measurable manner?	7		
2	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4		
3	Were variable estimates used in the analysis from the best available source (i.e., randomized control trial - best, expert opinion - worst)?	8		
4	If estimates came from a subgroup analysis, were the groups pre-specified at the beginning of the study?	1		
5	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9		
6	Was incremental analysis performed between alternatives for resources and costs?	6		
7	Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5		
8	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7		
9	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8		
10	Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term, and negative outcomes?	6		
11	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7		
12	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8		

13	Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7
14	Did the author(s) explicitly discuss direction and magnitude of potential biases?	6
15	Were the conclusions/recommendations of the study justified and based on the study results?	8
16	Was there a statement disclosing the source of funding for the study?	3
	Total Points	100

When interpreting QHES questions, points were only awarded if the reviewers believed that the most important criteria for the questions were met; if this was the case all points would be awarded. The reviewers did not award fewer points if the study only met some of the question's criteria, the response to each question either being a 'yes' (therefore full points) or a 'no' (no points). For individual questions on the QHES, there were particular criteria to be met in addition to those included within the QHES question. These were:

- Q5: *How was uncertainty handled?* – The reviewers required that uncertainty was investigated using robust statistical techniques; for within-trial evaluations, this was done by using non-parametric bootstrapping, and for modelling evaluations, PSAs were required. The reviewers deemed that one- and two-way sensitivity analyses did not capture uncertainty robustly enough for Q5 to be met and points awarded.
- Q8: *Did the time horizon allow for all important outcomes?* – Chapter 2 showed that smoking in pregnancy impacts on the health of mothers and infants both within-pregnancy and across their lifetimes. For points to be awarded, studies had to have included a within-pregnancy and lifetime analysis horizon for both mother and infant.
- Q10: *Were the major short-term, long-term and negative outcomes included?* – Chapter 2 identified that smoking in pregnancy is potentially-causally associated with nine conditions. If any of the following conditions was omitted from the evaluation, no points were awarded:
    - Placenta previa
    - Placental abruption

- Ectopic pregnancy
- Pre-eclampsia
- Pre-term birth
- Early & late foetal loss
- SIDS
- LBW
- Respiratory illness

Although there is no established, standardised interpretation of the QHES score, we adopted the following grouping based upon the work by Spiegel et al [189]: 0-24, extremely poor quality; 25-49, poor quality; 50-74; fair quality; 75-100 high quality.

3.3.8 Data Synthesis

It may have been possible to meta-analyse effectiveness and cost data to generate pooled estimations of incremental effectiveness and costs, allowing an ICER to be calculated across all studies. However, it was anticipated that this would be inappropriate due to the high degree of variation in interventions and population across all studies, and would not produce a meaningful result. Another possibility would have been not to conduct a meta-analysis, but convert costs in the same currency and price year to allow comparison across all the studies as to which interventions appeared to be cost-effective. However the primary aim of this review was to critically assess previous evaluations to identify the potential short comings of the current literature, and therefore this analysis was deemed superfluous to addressing this question.

We adopted a narrative synthesis with the primary objective of discussing the quality of the methods used in identified studies, as determined by the QHES. The results of the assessment from the QHES would be used to demonstrate the strengths and weaknesses of each individual study and of the literature as a whole. To facilitate this we allocated QHES scores to studies as an indicator of overall study quality and qualitatively inspected the components of studies' scores to investigate which aspects of evaluation quality were commonly absent or poor across studies.

3.4 **Results**

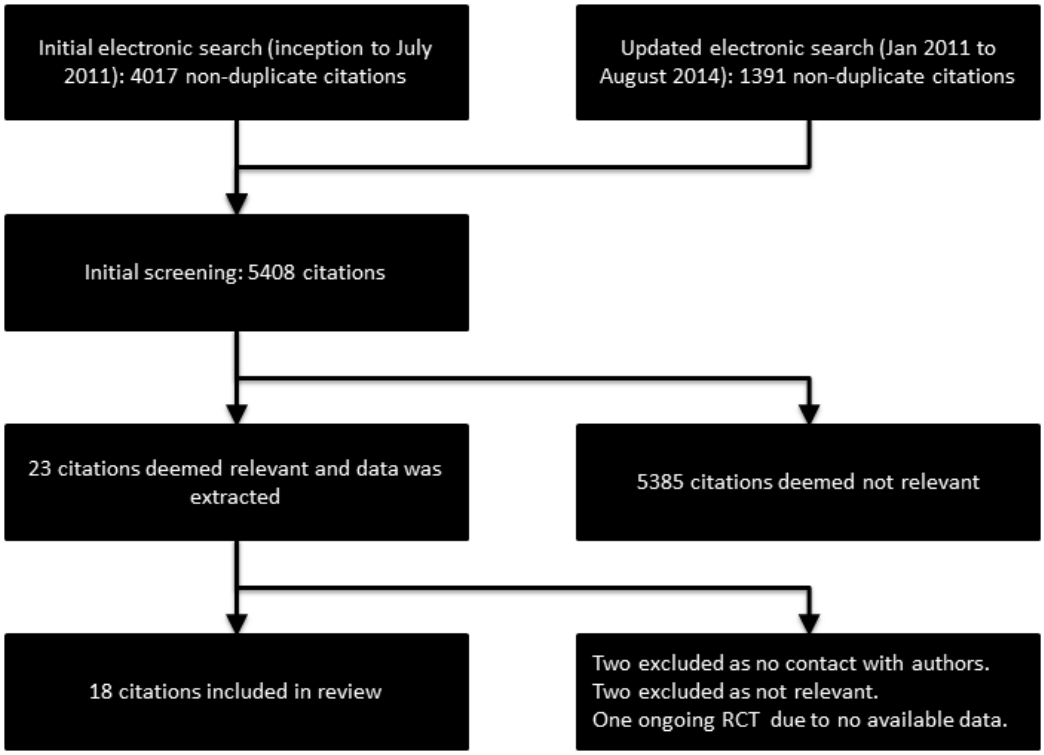
Searching until 2011 returned 3,986 citations; a further 31 potential studies were identified from the NICE website. The US Surgeon General website returned no potential studies. Of the 4,017 citations, the first stage of screening identified 18 studies to be included in the full review (see Figure 3.1). The updated search identified a further 1,391 citations. Screening identified one further study for inclusion, undertaken as part of NICE guidance. [190] The initial search identified one RCT which was ongoing [191], and the update identified three ongoing RCTs. [192-194] Contact with the trials' principal investigators returned the unpublished data for three RCTs [123, 195, 196], while one was unavailable. [193] Two of the initial 18 studies were identified as conference abstracts. [197, 198] Further searching failed to uncover a full economic report associated with these abstracts, and attempts to contact the authors failed, hence they were excluded.

Two further studies were excluded during data extraction. One study investigated the cost-effectiveness of training general practitioners to deliver cessation interventions, and the main outcomes (acceptance of a training session, purchase of cessation materials, and use of the materials) were not related to cessation or pregnancy. [199] The other was found not to have a relevant cessation intervention. [200]

18 studies were included in the full review. 13 studies were published in peer reviewed journals [65, 68, 69, 71, 137, 201-208], two with NICE guidance [139, 190], and three were unpublished RCTs. [123, 195, 196]

After considering included studies, it was decided that meta-analysis was inappropriate because studies were of an extremely heterogeneous nature, and questions posed by the review could probably be satisfactorily answered by narrative review; therefore this was deemed more appropriate.

Figure 3.1: Review PRISMA diagram



3.4.1 Characteristics of Studies

Appendix 12.3, Table 12.3 and Table 12.4 report the key characteristics of included studies. Nine studies were CBAs [65, 68, 69, 201, 203-205, 207, 208], five were CEAs [71, 123, 195, 202, 206], three were CUAs [137, 139, 190], and one had both a CEA and CUA. [196] There was a wide variety of interventions. Three studies used a telephone-based intervention [201, 202, 206], one combined telephone and self-help materials [137], and one used financial incentives linked with UC. [196] Two used self-help materials [203, 208], while one study combined self-help materials and counselling. [69] Two studies used counselling interventions [201, 207], and four studies used hypothetical interventions. [65, 68, 71, 205] One study used multiple interventions identified from a systematic review [139], while another used interventions described in the literature. [190] One study investigated NRT versus placebo, both combined with behavioural support [123]; another compared physical activity with behavioural support versus behavioural support alone. [195] Comparators in all except one study were either no intervention or UC, which had varied definitions across studies. [123]

Nine economic analyses were part of clinical trials [69, 123, 137, 195, 196, 202-204, 208], four were part of observational studies [71, 201, 206, 207], and five were hypothetical studies based upon data in the literature. [65, 68, 139, 190, 205] 12 studies took a healthcare provider perspective for the analysis, while six studies undertook a societal one. [123, 137, 139, 190, 195, 196]

Most evaluations used short time horizons for the analyses, with 10 studies considering only outcomes during pregnancy or immediately afterwards, while six reported considering outcomes over the mother's lifetime [68, 69, 137, 139, 190, 196], and two studies considering the lifetime of the infant as well. [139, 190] One study incorporated healthcare costs associated with the first year of life of the infant [137], while another included NICU healthcare costs for LBW in the immediate postpartum period. [196] Six reported discount rates, with rates of 3% [137], 3.5% [139, 190, 196], 4% [68], and 5%. [71] Cost data was predominantly obtained from micro-costing analyses, and tended to be limited to costs associated directly with the intervention (salary, materials, etc.). These tended to be collected as part of the trials, or taken from reliable cost sources if not. Costs associated with LBW births and other infant outcomes were generally taken from the literature.

Measures of smoking cessation were the most frequent primary outcomes (12 studies), while two studies used numbers of LBW infants prevented [68, 205], one used SIDS prevented [71], and three used QALYs. [137, 139, 190] Secondary outcomes were: LBW infants (six studies) [65, 69, 123, 137, 203, 204], premature birth (two studies) [65, 203], prenatal death (three studies) [68, 123, 139], life years (LY) (one study), [137], and QALYs (one study). [196] When smoking status was used as an outcome in trials, this was biochemically validated in eight studies. [69, 123, 137, 195, 196, 201, 206, 208] Deterministic sensitivity analyses, investigating assumptions made in economic analyses, were performed in ten studies [65, 68, 69, 137, 139, 196, 201, 205, 206, 208]; the most frequently- varied parameters were intervention effectiveness [65, 68, 69, 137, 201, 205], intervention cost [68, 69, 137, 139, 201, 206, 208], and background quit rate. [65, 205] Four studies reported using robust statistical techniques in the sensitivity analysis. [123, 190, 195, 196]

3.4.2 Findings of included studies

Five studies were conducted in the UK. [123, 139, 190, 195, 196] All other studies were conducted in the US. All except one concluded that smoking cessation interventions were cost-effective or cost-beneficial. [137]

Of three UK RCTs, the incremental cost per quitter was £4,926 for NRT [123], and £1,127 for financial incentives [196], while the other found the physical activity intervention was more effective and cheaper than UC. [195] Although one RCT did collect EQ-5D data, there was no statistically significant difference between the two groups, and therefore no analysis was performed using these data. [123] One RCT extended the within-trial results to lifetime horizon for the mother using a previously developed model [209], and estimated an incremental cost per QALY of £482 for financial incentives. [196]The impact of uncertainty was explored in all RCTs, with Cooper et al finding the majority of the bootstrapping iterations laid within the north east quadrant, suggesting that NRT was likely to be more effective but more costly. [123] However, there was a lot of uncertainty in the cost estimates which meant that the iterations were spread around all four quadrants of the cost-effectiveness plane. Tappin et al explored uncertainty using a PSA [196], which suggested that at a willingness to pay of £20,000-£30,000 per QALY, the probability of the financial intervention being cost-effective against UC was 70%; however there was also some degree of uncertainty, with iterations spread across all four quadrants of the cost-effectiveness plane. Furthermore, a value of information (VOI) analysis suggested that at a willingness to pay of £30,000, additional research was potentially worthwhile if it cost less than £3.3 million. Ussher et al found that at a willingness to pay of £20,000 per QALY, approximately 75% of iterations were cost-effective, but this never went above 80%. [195]

One modelling study reported the largest ICER, of £4,005 per QALY, being associated with cognitive behavioural therapies (CBTs). Both rewards (interventions where the participant received a financial or non-financial reward for meeting certain criteria) and 'other interventions' (non CBT, financial, or pharmacological interventions) were found to be dominant over no intervention, while pharmacotherapies had an ICER of £2,253 per QALY, feedback had an ICER of £1,992 per QALY, and stages of change (SoC) interventions an ICER of £3,033 per QALY. [139] The other modelling study found that, even considering short-term (defined as three year post intervention), cessation interventions appeared to be

cost-effective with ICERs of £5,445 and £1,331 per QALY for high versus low intensity behavioural support, £17,827 and £157,696 for high intensity versus UC, and £41,088 and £60,409 per QALY for conditional versus non-conditional incentives. [190] The ICERs decreased as the perspective was increased to include the lifetime for both the mother and her infant. The PSA results suggested that all the interventions modelled achieved a 100% probability of cost-effectiveness by £31,000 per QALY in the lifetime analysis. The implication of these findings is that cessation interventions are cost-effective in the UK setting.

One US study reported that their MVI intervention reported no additional benefit in QALYs, suggesting that the intervention was not cost-effective. [137] However, other studies in the US found cost-benefit ratios estimated from 2:1[204] to 2.8:1[203], though one study found the cost-benefit ratio to be between USD 1:17.93 to USD 1:45.83. [69] Another study found an effectiveness to cost ratio of USD 1:84 [206], while one suggested that long-term costs averted were USD 3.26 for every USD 1 spent on cessation interventions. [68] Neonatal cost savings of USD 881 (£523.67[24]) per maternal smoker were identified in a separate study, which found that an intervention costing USD 24 (£14.27[25]) per smoking mother would generate a net saving of USD 8 million (£4,755,200[26]) in healthcare costs nationally in the US [201]. Pollack et al estimated that a USD 45 (£26.75[27]) intervention would annually avert 108 SIDS at an estimated cost of USD 210,500 (£125,121.20[28]) per life saved. [71] Another study suggested that the breakeven cost of the intervention was USD

[24] Converted 3rd August 2014 USD 1 = 0.5944, http://www.dollars2pounds.com/ExchangeRate/USD/GBP

[25] Converted 3rd August 2014 USD 1 = 0.5944, http://www.dollars2pounds.com/ExchangeRate/USD/GBP

[26] Converted 3rd August 2014 USD 1 = 0.5944, http://www.dollars2pounds.com/ExchangeRate/USD/GBP

[27] Converted 3rd August 2014 USD 1 = 0.5944, http://www.dollars2pounds.com/ExchangeRate/USD/GBP

[28] Converted 3rd August 2014 USD 1 = 0.5944, http://www.dollars2pounds.com/ExchangeRate/USD/GBP

32 (£19.02[29]) (varying between USD 10 and USD 237(£5.94 - £140.87[30])) [65], while another suggested that cessation interventions were cost-effective if they cost USD 80 (£47.55[31]) or less and achieved an 18% quit rate. [205] It was suggested by Thorsen et al that if the maximum spent was USD 15,366 (£9,133.55[32]) on an intervention, savings of USD 137,592 (£81,784.68[33]) in healthcare costs would be achieved. [207] ICERs in the US were estimated in two studies, with one calculating an ICER per quitter of USD 298.76 (£177.58[34]) [202], and the other estimating two ICERs per quitter of USD 50.93 (£30.27[35]) for one intervention and USD 118.83 (£70.63[36]) for the other. [208] Therefore, from the US perspective all studies except one suggest that cessation interventions delivered during pregnancy are potentially cost-effective.

3.4.3 QHES assessment

Table 3.2 summarises QHES assessment results. Six studies attained a score greater than 75 indicating high quality [65, 123, 137, 190, 195, 196], six were deemed of fair quality [68, 139, 202-205], and six poor quality. [69, 71, 201, 206-208] The median score was 58, with a range from 33 to 87, and an inter-quartile range of 38. Of the six high quality studies, four

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[29] Converted 3rd August 2014 USD 1 = 0.5944, http://www.dollars2pounds.com/ExchangeRate/USD/GBP

[30] Converted 3rd August 2014 USD 1 = 0.5944, http://www.dollars2pounds.com/ExchangeRate/USD/GBP

[31] Converted 3rd August 2014 USD 1 = 0.5944, http://www.dollars2pounds.com/ExchangeRate/USD/GBP

[32] Converted 3rd August 2014 USD 1 = 0.5944, http://www.dollars2pounds.com/ExchangeRate/USD/GBP

[33] Converted 3rd August 2014 USD 1 = 0.5944, http://www.dollars2pounds.com/ExchangeRate/USD/GBP

[34] Converted 3rd August 2014 USD 1 = 0.5944, http://www.dollars2pounds.com/ExchangeRate/USD/GBP

[35] Converted 3rd August 2014 USD 1 = 0.5944, http://www.dollars2pounds.com/ExchangeRate/USD/GBP

[36] Converted 3rd August 2014 USD 1 = 0.5944, http://www.dollars2pounds.com/ExchangeRate/USD/GBP

were the most recently completed studies, while the older studies tended to be of poor or fair quality.

Table 3.2: Results of the QHES assessment

Author	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Total
Ayadi	2006	X	X							X			X			X		35
Cooper	2014	X	X	X	X	X	X	X		X		X	X	X	X	X	X	87
Dornelas	2006	X		X			X	X		X		X	X	X		X	X	67
Ershoff	1983	X					X	X		X		X	X	X		X	X	59
Ershoff	1990	X	X	X			X	X		X		X	X	X		X	X	71
Hueston	1994	X					X	X				X	X	X	X	X	X	57
Mallender	2013	X		X		X	X	X	X	X		X	X	X	X	X		86
Marks	1990	X		X				X		X		X	X		X	X		57
Parker	2007		X					X		X		X			X		X	33
Pollack	2001	X						X				X			X	X	X	36
Ruger	2008	X	X	X	X		X	X		X		X	X	X	X	X	X	78
Shipp	1992	X	X	X			X	X		X		X	X	X	X	X	X	77
Tappin	2014	X	X	X	X	X	X	X		X		X	X	X	X	X	X	87
Taylor	2009	X					X	X		X		X	X	X		X		56
Thorsen	2004	X						X		X					X	X	X	37
Ussher	2014	X	X	X	X	X	X	X		X		X	X	X	X	X	X	87
Windsor	1988	X						X		X		X				X		35
Windsor	1993	X		X						X		X	X			X	X	49
Frequency		17	8	10	4	4	11	16	1	16	0	16	14	11	11	17	13	
Percentage		94%	44%	56%	22%	22%	61%	89%	6%	89%	0%	89%	78%	61%	61%	94%	72%	

X = yes on QHES

3.4.4 Qualitative assessment of individual components of economic evaluations

Qualitative assessment of individual QHES items (Table 3.2) indicates that almost all included studies had clearly presented objectives (Q1, 17 studies) and methodology for data abstraction (Q7, 16 studies); appropriate measurement of costs (Q9, 16 studies); used valid health outcomes (Q11, 16 studies); displayed an economic model clearly and transparently (Q12, 14 studies); had justifiable conclusions based on studies' findings (Q15, 17 studies) and disclosed sources of funding (Q16, 13 studies). No studies reported an inappropriate costing method; however, many did not report the year from which cost estimates were calculated, preventing the re-use of cost data in subsequent studies.

The following aspects of methodology were less comprehensively presented in evaluations: performance of incremental analyses (Q6, 11 studies), justification for choice of parameters used within economic models (Q13, 11 studies) and explicit discussion of potential biases from economic evaluations (Q14, 11 studies). Few studies used estimates for parameters obtained from sources judged to be the 'best available' (Q3, 10 studies), stated the perspective of economic analyses (Q2, eight studies), or specified sub-group analysis at the beginning of studies (Q4, four studies); however, most studies did not contain sub-group analyses, so this question has limited relevance. Outcome data were either collected within trials or estimated from the literature but, amongst studies using estimates, none used estimates derived from systematic reviews and, hence, literature sources used were not judged as being the best available evidence.

Only four studies performed a robust analysis of uncertainty, the rest either used deterministic sensitivity analyses or reported no sensitivity analyses (Q5). No studies were judged to have included all major short- and long-term maternal and foetal outcomes (Q10), though one study came close, omitting just premature birth. [190] Only one study was judged to have a time horizon that incorporated both the effects within-pregnancy and lifetime as well for both the mother and infant (Q8).

3.5 **Discussion**

This review found only 18 studies which included economic evaluations of cessation interventions delivered during pregnancy; only six of these (33%) were judged as high quality. Evaluations were generally well described, utilised appropriate health outcomes and drew realistic conclusions based upon their results, but significant aspects of analyses were deficient. Specifically, where estimated, smoking outcomes did not appear to be derived from the highest quality literature sources; no economic models comprehensively considered all major and relevant foetal and maternal health outcomes, only one employed an appropriate time horizon, four controlled for uncertainty of estimates using statistically robust methods, and only three studies reported a primary outcome measure using a generic health related quality of life outcome, such as QALYs.

3.5.1 Limitations of review

A limitation of this review is that the QHES is a subjective instrument, and some QHES questions might be considered open to different interpretations. This was highlighted by the need for discussion among reviewers to resolve occasional disagreements about how some QHES items related to studies. However, the other checklists identified in the scoping review were also subjective questionnaires and, therefore, this is likely to have been a problem with any quality checklist utilised. Furthermore, it has been suggested that the greatest influence on the quality assessment comes not from the utilised checklist but from the reviewer themselves. [210] We have attempted to avoid this issue by using at least two reviewers to assess the quality for each included study, however there is still potential for this to be an issue. Secondly, there were occasions where the reviewers felt QHES items were difficult to completely address and, rather than awarding all available points only for completely addressing a criterion and nothing for not doing so, rewarding partial achievement of QHES items could have been more appropriate. Certainly, other researchers have highlighted that certain questions on the QHES can result in ambiguous assessment. [211] For example, QHES question three deals with information sources, and it might be appropriate to score this item in a graded fashion with points awarded being dependant on the different types of study design which could generate information used in the evaluations (e.g. eight points for information from systematic review, seven for information from clinical trial and zero points for information from expert opinion). This

could have resulted in the points score calculated for each study better reflecting the overall quality of the methods used, potentially providing a more meaningful comparison. Finally, although the QHES is a good measure for the internal validity of the study, it does not measure external validity, and has not yet been demonstrated thus. [188] This means this review was unable to capture whether the results of the included studies could be generalised to the population, and hence a meaningful comparison across all the models may not be possible or appropriate. Nevertheless, we believe that our use of QHES is appropriate to identify, across studies, those aspects of economic evaluations which might require development.

Another potential limitation of the review is the inclusion of the additional specifications associated with questions five, eight, and 10 on the QHES instrument. This could have potentially added bias to favouring the improved economic model, suggesting that the conclusions from this review are prejudiced against the current literature. However, it is unlikely that these additional specifications are introducing bias, because they could be argued as critically important for any model/evaluation of cessation during pregnancy. For example, without performing a statistically robust analysis of uncertainty, it is impossible to say with confidence that the decision made on the basis of the evaluations results is the correct one. Furthermore, a deterministic analysis may just be a 'historical artefact' due to the included parameters, and in reality the intervention is not value for money, and hence we have foregone benefits that would have been gained by making the correct decision.[109] With regards to the time horizon and inclusion of major outcomes, how can it be concluded that an evaluation is correctly specified if it only focuses on within-pregnancy, excluding any long-term benefits of quitting and reductions in smoking attributable healthcare costs. This would suggest that the evaluation is incorrectly specified as it is not taking into account important benefits and healthcare costs, and hence any decision made on the results of this evaluation could be incorrect. Considering these pitfalls, the author believes that these additional specifications to the QHES are a necessity and do not introduce bias into this review.

One final limitation is that there are possible issues with the QHES scoring system. The use of the scoring system is debatable in the literature, with some researchers suggesting that the advantage of a scoring mechanism is questionable. [211] Certainly, scoring systems in the quality assessment of RCTs have been brought into question, with criticisms

highlighting the lack of standard techniques and/or rigour in the development of the scales [212, 213], and that the scale used and whether the reviewers are blinded or open to authorship of the trial can greatly influence the quality assessment weighting in the meta-analysis. [214, 215] Hence, it is likely that these issues also persist with the QHES scoring mechanism, although the QHES scoring mechanism was subsequently demonstrated to be valid after it was trialled on a group of 60 experts (30 health economists and 30 clinicians) across three disease states [183, 186], so it is unclear how much of an issue the use of the scoring mechanism is in this context. Additionally, it may be possible that high quality information has been eliminated from what has been considered an overall poor scoring study. This could be an issue, although it is difficult to determine how much impact this may have on the conclusions of this review. However, the focus of this review was to determine the limitations of the current literature, and not to inform on which interventions were considered the most value for money. As such, the QHES scorings do not influence the conclusions of the review, since the QHES was used to highlight the potential methodological fallings of previous evaluations, and thus the scoring is unlikely to bias the conclusions of this review.

3.5.2 Strengths of review

This review also has two important strengths. The broad search strategy has allowed the review to identify the majority of the literature published, and it is unlikely that an evaluation has escaped being identified. The review has also incorporated the more recent literature that had been published since the previous review. Therefore, this review is the most comprehensive in this subject to date.

The use of the QHES has allowed a systematic identification of the shortcomings in the published evaluations. This is crucial for the improved model to be developed later in this thesis, since the review has identified the most important issues which need addressing for the new model to be an improvement on the previous literature. The important impact of identifying the shortcomings of the current literature is that the review demonstrates that the included studies are potentially inaccurately estimating the cost-effectiveness of cessation interventions. This would suggest that there is potentially misinformation being used in the decision-making process for healthcare interventions across the globe, with the increased chance that the wrong decision is being made. However, the current literature

does suggest that within-pregnancy cessation interventions are potentially cost-effective, so it is unlikely that an improved model will change this decision. But, the current literature cannot inform the decision maker as to how confident he/she may feel that delivering within-pregnancy cessation interventions is the correct decision. Furthermore, an improved economic model may take more outcomes into account which may be seen as relevant to the decision maker, and hence he/she may feel that the improved model is producing more robust estimates of the cost-effectiveness of cessation. This is an important justification for constructing an improved economic model.

3.5.3 What is well established in the previous literature?

The previous literature currently demonstrates that cessation interventions are generally cost-effective, particularly when considering incremental costs per quitter. Only one study found that cessation interventions during pregnancy were not cost-effective [137], all other studies estimating relatively low costs per quitter or benefit cost ratios of approximately 3:1. Studies estimating incremental costs per quitter found that either the interventions were dominant over UC or reported relatively low values, mostly less than £5,000. This would suggest that, should the parameter of interest be the number of quitters generated by intervention, or the incremental cost per quitter, then this is already well established in the literature, requiring no further exploration.

The costs involved with delivering an intervention have also been well explored in the previous literature. Out of the 12 studies which were conducted as part of an RCT or other observation study, 10 can be classified as having micro-costed the intervention included in the study. This is important because having accurate costs involved in delivering the intervention is required for demonstrating the cost-effectiveness. Inaccurate cost data is highly likely to generate inaccurate cost-effectiveness estimates. Determining accurate costs of interventions is also important for any hypothetical decision analytic model, since these can be used to model and estimate the longer term impacts of interventions, which would be difficult to capture within the short time frame of an RCT. However, while studies seemed to collect appropriate cost data, several did not report the prices used in the analysis, which can make reutilising these costs in subsequent estimations very difficult.

3.5.4 What requires improvement in the previous literature?

Few studies reported using a generic HRQoL measure, with only four studies reporting incremental costs per QALY. [137, 139, 190, 196] One RCT collect EQ-5D at six months postpartum, but, due to insignificant differences between the intervention and control group, did not perform any analysis of this data. [123] Generic outcomes, like QALYs, can incorporate both patients' quality of life and life expectancy measures and are used by health providers to compare the benefits and costs of interventions which affect very different clinical conditions. Consequently, although the previous literature allows comparison between cessation interventions, the same comparisons cannot be made across the healthcare sector as a whole. This is very important for decision makers as they might be considering whether to fund cessation interventions in the context of a whole mix of interventions, and therefore the cost-effectiveness needs to be demonstrated using a standardised measure. The results of the included studies were mixed, with two suggesting that interventions were cost-effective, while one did not; therefore this requires further exploration.

Most studies focused on a within-pregnancy time horizon, with only four studies considering the impacts of smoking during pregnancy on longer term outcomes [137, 139, 190, 196], and one of these seems to be relatively constrained as to what longer term included. Smoking has serious health effects, both within pregnancy and general morbidities. Doll et al has demonstrated that smoking in general increases the risk of morbidities such as lung cancer and CHD, as well as increasing the general mortality rate compared to non-smokers. [66] Within-pregnancy, smoking increases the risks of several conditions, including ectopic pregnancy, miscarriage, and placental abruption. [2, 3] After pregnancy, smoking both within-pregnancy and after have also been demonstrated to impact on the health of the offspring, with increasing risks associated with respiratory diseases. [216] Therefore, to determine the cost-effectiveness of smoking cessation during pregnancy, the time horizon must not only capture within-pregnancy impacts, but also impacts over the lifetime, for both mother and infant. Most of the previous literature was trial-based, and estimated outcomes in keeping with the trial follow up period; however one trial extended their analysis using a Markov model to estimate the impact on the maternal lifetime QALYs and costs. [196] Of the decision analytic models, three focused on within-pregnancy impacts [65, 68, 205], while two looked at a broader time horizon. Taylor explored some of the impacts on both the mother's and infant's lifetime [139], but did not

take into account any within-pregnancy impacts. Ruger et al extended the results of the trial to a lifetime perspective using published estimates, but did not estimate any health related costs for the infant beyond the first year of life. [137] Only Mallender et al seem to develop a model which incorporated some of the impacts both within-pregnancy and across the lifetime. [190]

Tied in with the time horizon problem, many studies were missing key conditions related to smoking in pregnancy. Most studies omitted maternal co-morbidities associated with smoking and pregnancy, e.g. placental abruption, placenta previa, pre-eclampsia. These can all lead to severe complications during pregnancy, and in a worst case scenario, death to the infant, the mother, or both. Of the within-pregnancy studies, only Shipp et al appeared to include maternal complications [65], although they are also likely to be captured within some of the RCTs. [123, 195, 196] Furthermore, birth and lifetime conditions for the infant were not included in many of the studies. From Chapter 2, smoking has been causally associated with premature birth, LBW, asthma, etc. Several studies attempted to capture the healthcare cost savings for adverse birth outcomes avoided from cessation [68, 69, 71, 201, 203-205, 207], but only one study included the impact of LBW and asthma on the health of the child across their lifetime. [190] Unfortunately, this study excluded premature birth.

Only four studies considered women's relapse to smoking after pregnancy. [137, 139, 190, 196] Very different rates of relapse were used; Ruger et al suggesting that 35% have relapsed over their remaining lifetime, while Taylor used 70% within one year postpartum. Tappin et al assumed a relapse rate of 60% and 30% in the intervention and control arms respectively [196], before applying longer term relapse probabilities for up to eight years after the intervention (5% per annum between years one and five, and 3% per annum between years six and eight) from studies of non-pregnant populations. Mallender et al did not use relapse per se, but estimated the number of women who would quit for good in any one year. Therefore, for one year after intervention, the one year quit rate as estimated in that particular intervention's study was utilised, while a background quit rate of 2% was used at all other times. This lack of consistency suggests that relapse to smoking post-pregnancy is underexplored in the previous evaluations.

An important implication is that the mother's direct health risks from smoking increases with increasing relapse, as does the infant's exposure to second-hand smoke with the acknowledged health risks this entails. [24] Additionally, recent work suggests that if their mother smokes, an infant is over twice as likely to become an adult smoker [25], potentially exposing him or her to the associated lifetime adult health risks. Hence, by not including a rate of relapse to smoking after childbirth, most economic models are overestimating the number of mothers who remain abstinent after pregnancy, potentially overestimating the benefits of smoking cessation.

A further issue is that the number of studies which robustly control for uncertainty is very low, with only the four most recently completed actually incorporating any statistically robust techniques. [123, 190, 195, 196] Controlling for uncertainty is important since it demonstrates that the correct decision has been made based on the results of the evaluation. Whilst in the past one- and two-way deterministic sensitivity analyses have been used for gauging the impact of uncertainty, these cannot control for the impacts associated with the uncertainty surrounding all parameters. [109] This is where a PSA is required. Two studies reported using a PSA, although Mallender et al only varied costs and quit rates for the interventions. [190] Tappin et al performed a broader PSA [196], covering the intervention costs, quit and short-term relapse rates, QALYs, and long-term disease costs, but not longer term relapse rates. Therefore, the capturing of uncertainty is potentially limited in the previous literature.

3.5.5 The influence of the review on the design of the new improved economic model

Although the current literature does not seem to have a definitive model structure for evaluating the within-pregnancy impacts of cessation, there are several previously published models which do have some influence on the structure of the mother's lifetime component of the new improved economic model. Taylor, Mallender et al, and Tappin et al used Markov simulation for the long term impacts of cessation on the health of the mother. [139, 190, 196] Each of these models used Markov cohort simulation with states based around smoking behaviour (current smoker, former smoker, etc). It would seem pertinent that adopting a similar structure for the mother's lifetime component would be appropriate, although it may be necessary to alter the structures slightly to better suit the

improved economic model. Such structure alterations will be the focus of Chapter 6, which introduces the Markov model for the mother's lifetime.

3.5.6 Implications of the review

Although there appears to be ever more literature on evaluations of cessation interventions during pregnancy, the required information for making decisions is still limited. There is strong evidence for cost per quitter outcomes, but comparable measures taking into account HRQoL have not been investigated. Furthermore, many of the models do not take into account the appropriate time horizons, focusing on within-pregnancy impacts, and excluding many of the important morbidities associated with smoking during pregnancy. This would suggest that the previous literature is not capturing the cost-effectiveness of smoking cessation during pregnancy completely, and therefore could be misinforming decision makers, certainly around the probability that the decision is the correct one. This review has several important implications for the improved economic model:

- Outcomes should be measured using some generic measure of HRQoL
- The model should incorporate both the within-pregnancy and lifetime horizons for both the mother and infant, and therefore should include conditions both related to the mother and her offspring
- Accurate modelling and incorporation of smoking behaviour after pregnancy for the mother
- The model should include a PSA to control for uncertainty not only associated with the intervention, but with the included parameters as well

3.6 **Summary**

Given that smoking during pregnancy is an important public health issue, there are relatively few high quality economic evaluations demonstrating the cost-effectiveness of cessation interventions. There is a clear need for further evaluations to be conducted in this area. The next chapter investigates relapse after pregnancy, with the aim of addressing one of the key issues highlighted by this review.

Chapter 4: Smoking abstinence in the postpartum period after receiving a smoking cessation intervention: A systematic review

4.1 Introduction

Although studies have investigated postpartum smoking behaviour, estimates of relapse to smoking after pregnancy vary. It has been estimated that 19% to 62% of women who stopped smoking in pregnancy have relapsed by three [217-223], 30% to 76% by six [217, 221, 223-231], 32% to 59% by 12 [221, 227, 232, 233], 77% by 18 [234], and 59% by 24 months postpartum. [235] Rattan et al investigated much later relapse in a longitudinal cohort study which had up to 21 years follow up. [230] Self-reported smoking using seven-day point prevalence abstinence was reported at end of pregnancy, six months postpartum and five, 14, and 21 years after childbirth. Estimates for relapse were 43.5% at five, 35.5% at 14, and 35.8% at 21 years after childbirth. This variability amongst estimates for relapse to smoking in the postpartum period makes it difficult to choose a meaningful estimate for relapse rates to be used in economic models of cessation during pregnancy. A systematic review could help produce more accurate estimates of relapse in the postpartum period. This would be important, not only for predicting the smoking behaviour of mothers after pregnancy in general, but to investigate whether there are any differences in relapse behaviour between women who receive different cessation interventions in pregnancy, as any such differences could impact on interventions' cost-effectiveness. To the author's knowledge, no systematic review of smoking rates after pregnancy has been published. Consequently, in this chapter a systematic review and meta-analysis is undertaken to determine patterns of abstinence from smoking in the postpartum period.

4.2 Aims and Objectives

4.2.1 Primary aim:

To describe the rates of abstinence from smoking at different time points as far as possible after childbirth amongst women who attempted to quit smoking during pregnancy.

4.2.2 Objectives:

1) To systematically search for and identify RCTs in which pregnant smokers receive a smoking cessation intervention
2) To derive pooled estimates for the point prevalence of abstinence at different time points in the postpartum period
3) To investigate whether or not pooled estimates for the point prevalence of abstinence vary with intervention/experimental and control/no intervention groups.

4.3 **Methods**

4.3.1 Rationale for studies' inclusion

It was anticipated that the most robust data on the rates of abstinence from smoking after pregnancy would be reported by clinical trials. Two Cochrane reviews have been conducted investigating psychosocial interventions and pharmacological studies. [27, 28] Both these reviews use a maximum sensitivity electronic and manual search of the available literature. It is highly likely that both these reviews will have identified all relevant trials, both published and ongoing, and therefore it was felt that any additional electronic searching would not have increased the sensitivity of the literature search, and hence was deemed unnecessary. All included and excluded studies that were cited in both Cochrane reviews were screened for inclusion in this systematic review. For any ongoing trials, the protocol was screened to determine whether the study included any postpartum follow-up, and contact was made with the trials' principal investigator where necessary to determine if there were any available results.

4.3.2 Participants

Pregnant smokers in any care setting were included.

4.3.3 Interventions

Any intervention(s) aimed to encourage smoking cessation or prevent relapse to smoking during pregnancy. Control group participants could receive a placebo, another cessation intervention, or no intervention.

4.3.4 Outcomes

Quit rates; rates of point prevalence of abstinence from smoking. Rates reported at end of pregnancy and at least one other time point in the postpartum period. Biochemically validated and self-reported smoking cessation outcomes were considered.

4.3.5 Study design

Randomised and quasi-randomised controlled trials were included.

4.3.6 Exclusion criteria

Studies were excluded if:

1) The intervention was delivered to women who were pregnant but not currently smoking
2) Studies presented data in a format that could not be analysed and further information was not forthcoming from authors.
3) Interventions were delivered only to smokers who had already quit (usually relapse prevention interventions) or studies enrolled both smokers and recent quitters with outcomes reported together.
4) Studies reported smoking outcomes in the postpartum period, but not at end of pregnancy.

4.3.7 Data extraction

Identified articles were screened by two reviewers and those deemed relevant were retrieved in full; two reviewers independently extracted data and performed quality assessments, discussing any discrepancies until agreement was secured. Data extracted from the studies included:

- Trial design: country, trial year(s) , randomisation method
- Participants' characteristics
- Description of control and experimental interventions, intervention provider, intervention intensity
- Outcomes: abstinence rates in pregnancy four to eight weeks after randomisation, at the end of pregnancy and any time points afterwards; method of biochemical validation and any cut-off point and which, if any, participants were excluded from statistical analyses, with any justifications provided for this.

4.3.8 Quality assessment

Quality assessment was conducted by two reviewers using the Cochrane 'Risk of bias' tool developed by Higgins et al [236], with the following two modifications. Under the heading, 'Attrition bias', a section was added to incorporate whether the statistical analysis had been conducted on an intention to treat basis (i.e. assuming that participants lost to follow up were smoking), or whether any randomised participants had been excluded from the analysis. Secondly, under 'Other bias', a section was added to record whether biochemical validation had been undertaken, if the results were useable and if the validation had been done in an appropriate manner, i.e. had been conducted consistently (i.e. on all participants who either reported abstinence from smoking or all participants in the trial), and without bias towards certain types of participants. The risk of bias tool can be found in Appendix 12.4.

4.3.9 Data synthesis

Initially it had been intended to calculate relapse to smoking in the postpartum period, as this would be the most relevant information required for any improved economic model. However, during the data extraction phase, it became clear that the required longitudinal data (i.e. women reporting abstinence at the end of pregnancy being also followed up in the postpartum period) was unavailable. Data was available about the postpartum smoking behaviour of all participants in trials. This is different to relapse data since it gives a pooled abstinence estimate for those who were smoking at the end of pregnancy and those who were not, and we are unable to tell if the women reporting smoking abstinence at later postpartum time points are the same who reported abstinence at the end of pregnancy. Therefore, the primary outcome from the meta-analysis was abstinence from smoking amongst all trial participants using seven day point prevalence estimates; this is why findings are described as abstinence patterns rather than relapse curves.

Currently the two most common approaches for performing meta-analyses are fixed-effects and random-effects. In a fixed-effect model we assume that there is one true effect size which is shared by all included studies, hence we can hypothesize that the combined effect is the estimate of this common effect size. [237] Therefore, we can assign weights to all studies based entirely on the amount of information captured by that study; the larger the study, the greater the weight it carries in the meta-analysis. It is assumed that the only error between the observed effect size and the true population effect size is caused by within-study estimation error. However, in a random effects meta-analysis, we assume that the true effect can vary from study to study (e.g. effect size maybe higher if the subjects are older), therefore the studies included in the meta-analysis are considered to be a random sample of the distribution of effects, with the pooled estimate assumed to be the mean effect of this distribution. [237, 238] Because a random-effects model is trying to estimate the mean of a distribution of true effects, weights assigned to included studies are more balanced, hence small studies are not trivialised and large studies don't dominate the analysis. The random-effects model now controls for errors in both the within-study estimate of the true mean in a specific population and also the mean effect of all the true effects across different studies.

A random-effects (DerSimonian and Laird) meta-analysis was adopted. [238] This was because it was anticipated that there would be great deal of heterogeneity between included studies, since cessation interventions across trials were likely to vary not only in the pregnant population but also in intensity of the intervention. Furthermore, for the economic model, gaining information on the distribution of relapse estimates as generated by a random-effects analysis would be more useful when controlling for uncertainty than the point estimate generated by the fixed-effects analysis. A meta-analysis using intention to treat was conducted, synthesising weighted proportions of point prevalence abstinence rates, representing a summary measure of prevalence of abstinence at that time point. The results are presented as pooled proportions of smokers who were abstinent, with 95% CIs at the different time points; statistical heterogeneity between trials was quantified using the I^2 statistic.

To calculate the pattern of abstinence from smoking in early pregnancy until after pregnancy, it was necessary to identify appropriate time points for data aggregation. This was achieved by tabulating all time points at which smoking status was ascertained in included studies and then selecting those which were reported most. Where studies did not report smoking status at the selected time points, their data were allocated to the selected time point closest to the actual reported data collection time. To avoid potential heterogeneity generated by combining smoking data from time periods, the time points used to derive pooled estimates reflected those used by most individual trials. This resulted in review time points being relatively close together immediately after pregnancy, and then more spread out later in the postpartum period.

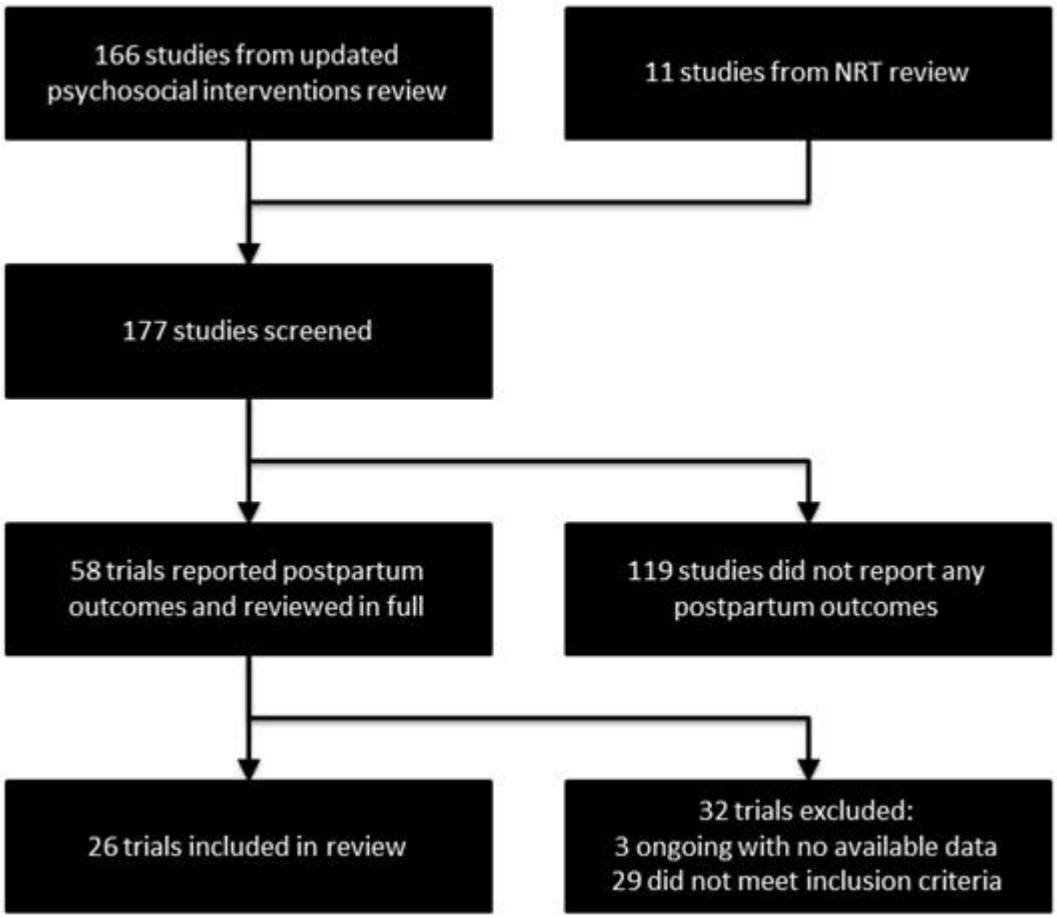
The primary analysis involved pooling all participants from both the control and intervention groups to give a pattern of abstinence for all participants in the postpartum period. Furthermore, the primary analysis included both validated and self-reported abstinence. A secondary analysis was conducted by splitting control and intervention participants to explore whether there were differences in postpartum smoking behaviour between groups. Finally, a sensitivity analysis was conducted using biochemically-validated abstinence data only to explore any potential bias caused by self-reported abstinence. Meta-analyses and abstinence pattern graphs were generated using Stata 11.2 [239], and the risk of bias summary drawn in Review Manager 5. [240]

4.4 **Results**

The two systematic reviews [27, 28] on interventions for smoking cessation during pregnancy identified 177 trials which potentially provided data on abstinence during and after pregnancy. Of these, 13 were ongoing, and screening was performed using manuscripts describing each trial's protocol. Initial screening reduced this to 58 studies which potentially reported outcomes in the postpartum period (see Figure 4.1). Four studies were identified as ongoing; contact with trials authors was unsuccessful for two trials [241, 242], one had completed but no results were available [193], and one had completed and the data was shared. [192, 195] During data extraction, 29 studies were excluded; details of which are given in Appendix 12.5, Table 12.5. 26 studies were included in this review, giving a cohort of 10,942 pregnant women. Characteristics of included studies are summarised in Appendix 12.5, Table 12.6.

19 studies were RCTs [123, 195, 202, 243-258], five were cluster trials [259-263], and two were quasi-randomised. [264, 265] Control interventions were predominantly information booklets, with these being used in 15 studies. [202, 246-250, 253, 254, 257-260, 262, 264] Eight studies used counselling [123, 195, 251-254, 258, 261], three used placebo patches [123, 252, 258], one used non-contingent vouchers (rewards given to participants for attending the clinic) [250], and one did not report what the control intervention was. [255] Three studies reported the control intervention to be UC while not defining what UC involved. [243, 256, 263] One study reported that the control group received no intervention. [244] For the intervention groups, 17 studies reported using information booklets [202, 243, 245, 247-250, 254, 256-262, 264, 265], 20 reported using counselling [123, 195, 202, 243-248, 251-254, 256-261, 265], four used NRT [123, 252, 253, 258], three used social support interventions [248, 251, 259], and two used MVI techniques. [255, 263] The following interventional approaches were employed in one study each: 'stages of change' intervention [262], financial incentives [249], contingent vouchers (where the smoker was rewarded for meeting certain criteria) [250], letters of support [255], and physical activity. [195] However, in most trials the experimental intervention was a combination of different techniques, with only four studies reporting using an individual technique for the experimental intervention. [244, 246, 263, 264] In the control group, 14 studies reported using a single technique for the control intervention. [243, 245, 247-249, 251, 253, 256, 257, 261-265]

Figure 4.1: Review PRISMA diagram



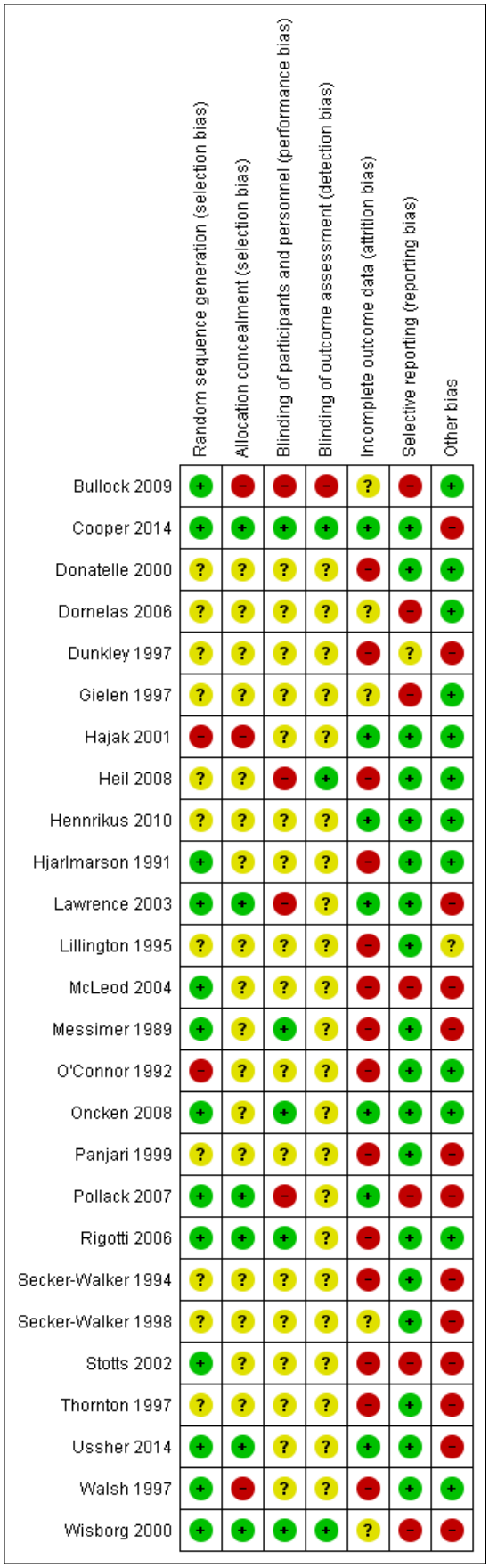
4.4.1 Risk of bias assessment

The results of the risk of bias assessment are given in Figure 4.2. On the whole, the quality of the included studies was judged poor, with many not reporting the necessary information required to make an adequate judgement. Nine RCTs reported using computerised randomisation [123, 195, 248, 252-255, 257, 258], but 10 gave insufficient details about this. [202, 243-247, 249-251, 256] Two cluster RCTs reported using computerised randomisation [262, 263], one used the drawing of folded tags [259], and one did not state the method of cluster randomisation. [260] One quasi-randomised study was randomised by the days of the month a participant was born [264], while the other was by alternate day of the week. [265] Only six studies reported adequate concealment [123, 195, 253, 254, 258, 262], while three studies demonstrated inadequate concealment.

[248, 257, 259] 17 studies did not provide enough evidence on whether the concealment was adequate or not.[202, 243-247, 249-252, 255, 256, 260, 261, 263-265] Only four studies reported adequate blinding of participants [123, 252, 258, 261], with four studies reporting no blinding [248, 250, 253, 262], and 18 studies did not provide enough evidence for a judgement to be made. [195, 202, 243-247, 249, 251, 254-257, 259, 260, 263-265]

An intention to treat analysis was not conducted in 23 studies. [202, 243-250, 254-257, 259-261, 263-265] Common reasons for the exclusion of participants were miscarriage, premature birth, loss to follow up, lost samples, moved hospitals/areas, refused to participate, and delivered interventions to which they were not randomised. 17 studies reported using biochemical validation, either using salivary cotinine (five studies) [195, 245, 248, 254, 260], urinary cotinine (five studies) [246, 250, 251, 257, 265], carbon monoxide (six studies) [123, 195, 202, 246, 252, 259], salivary thiocynate (one study) [249], and blood thiocynate (one study). [264] For salivary cotinine, cut-off points varied between ≤10 ng/mL and ≤30 ng/mL, while for urinary cotinine it varied between ≤64 ng/mL and ≤500 ng/mL, with one study reporting ≤500 nmol/L. Cut-off points for carbon monoxide varied between ≤4 ppm and ≤10ppm. For salivary thiocyanate, the cut-off point was ≤100 ug/mL, and for blood thiocynate 100 ng/mL, which seemed to be an acceptable cut-off point compared to the other biochemical validation tests. There was evidence of selective reporting in eight studies. [202, 244, 245, 248, 253, 255, 258, 263]

Figure 4.2: Summary of the risk of bias assessment



4.4.2 Publication bias

Funnel plots were plotted and examined for evidence of bias in studies; these were done for all time points at which data were pooled; however, this was difficult due to the relatively small number of studies at later time points and, for some points, funnel plots could not be calculated. As all studies reported data at the end of pregnancy, Figure 4.3 is the funnel plot for the end of pregnancy.

Figure 4.3: Funnel plot of bias assessment

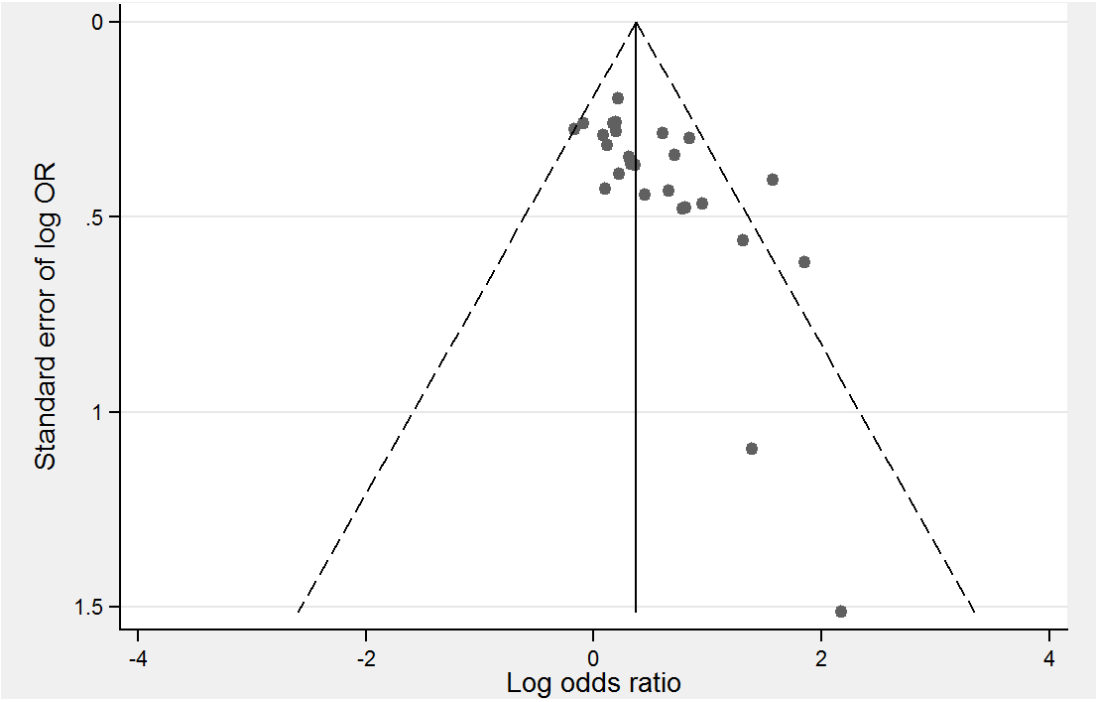


Figure 4.3 demonstrates that there is potential evidence of publication bias. There appear to be relatively few small studies included in the review, suggesting these studies have not been published. Another implication from the funnel plot is that published smaller studies tend to have higher estimates of abstinence compared to larger studies. This could also be explained by publication bias, suggesting that studies which appear not to achieve a high proportion of abstinence may be excluded from publication. However, the funnel plot also indicates a large degree of variation in the studies, suggesting a large amount of heterogeneity within the studies. This should be considered when interpreting the results of the meta-analysis.

4.4.3 Patterns of abstinence amongst all participants

Pooled proportions of abstinence were generated at four to eight weeks post-randomisation, end of pregnancy, and in the postpartum period at four, six and eight weeks; and three, six, 12, 18, and 24 months after childbirth. The results from pooling all participants are given in Appendix 12.6, Figure 12.1. The pattern of abstinence given in Figure 4.4 demonstrates that abstinence rates are at their highest at four to eight weeks post randomisation, before dropping slightly at end of pregnancy. In the postpartum period, abstinence would appear to decrease sharply at four weeks postpartum, but then increase again at six weeks and eight weeks postpartum, before declining as participants' progress through the postpartum period. The highest proportion of abstinence in the postpartum period occurred at eight weeks postpartum. There would appear to be a substantial decline in abstinence between three and six months, however the CIs of abstinence at these two time points considerably overlap.

4.4.3.1 Four to eight weeks post randomisation

Six studies reported data. [123, 195, 252, 253, 257, 258] The pooled proportion abstinent was estimated at 0.156 (95% CI 0.107 to 0.205). Heterogeneity was high with an I^2 of 92.2%, $p<0.001$.

4.4.3.2 End of pregnancy

All 26 studies reported data at the end of pregnancy. [123, 195, 202, 243-265] The estimated proportion abstinent was 0.126 (95% CI 0.107 to 0.146). The I^2 was 91.7%, $p<0.001$, suggesting a high degree of heterogeneity.

4.4.3.3 Four weeks postpartum

Two studies reported abstinence rates at four weeks postpartum [244, 262], the pooled proportion abstinent reported as 0.036 (95% CI 0.010 to 0.062). The I^2 was 66.0%, $p=0.086$.

4.4.3.4 Six weeks postpartum

Data was pooled from eight studies. [247, 248, 255, 257, 260, 261, 263, 265] The pooled proportion of abstinence was 0.118 (95% CI 0.085 to 0.152). The I^2 statistic was 88.5%, p<0.001.

4.4.3.5 Eight weeks postpartum

The pooled abstinence proportion was 0.136 (95% CI 0.113 to 0.159) among the two studies pooled. [249, 264] The I^2 was 0%, p=0.835.

4.4.3.6 Three months postpartum

Seven studies reported data at three months postpartum. [250, 251, 253-256, 258] The estimated pooled proportion abstinent was 0.111 (95% CI 0.070 to 0.152). There was a high degree of heterogeneity amongst studies, with the I^2 estimated at 87.8%, p<0.001

4.4.3.7 Six months postpartum

Data was pooled from 10 studies. [123, 195, 202, 245, 247, 250, 252, 255, 259, 263] The pooled abstinence proportion was 0.082 (95% CI 0.052 to 0.112). The I^2 was 94.9%, p<0.001.

4.4.3.8 12 months postpartum

The pooled proportion abstinent was 0.074 (95% CI 0.027 to 0.122) amongst the four studies reporting data. [123, 243, 246, 258] The I^2 was 95.5%, p<0.001.

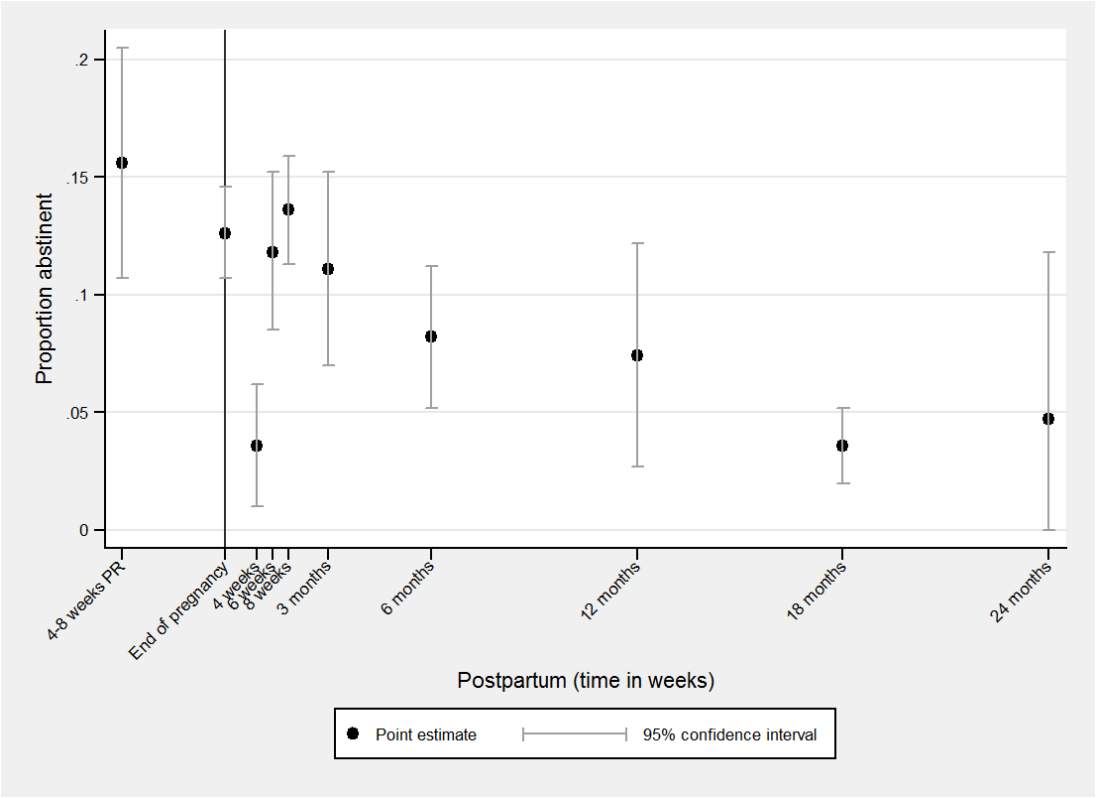
4.4.3.9 18 months postpartum

Two studies were pooled [243, 262], with the proportion abstinent estimated at 0.036 (0.020 to 0.052). The I^2 was 65.4%, p=0.089.

4.4.3.10 24 months postpartum

Two studies reported data at 24 months [123, 243], with an estimated abstinence proportion of 0.047 (-0.023 to 0.118). The I^2 was 98.2%, p<0.001.

Figure 4.4: Primary analysis: Pooled estimates of abstinence of all participants, from beginning of pregnancy [37]



4.4.4 Pattern of abstinence amongst control and intervention participants

To determine whether there was a difference in abstinence postpartum between intervention and control groups, a secondary analysis was conducted in which pooled abstinence estimates were split between the two. The results of this analysis are given in Appendix 12.6, Figure 12.2 and Figure 12.3. Figure 4.5 demonstrates the pattern of abstinence over time. The proportion of participants reporting abstinence is greater amongst intervention participants compared to control groups at all time points except one (18 months). Although intervention group abstinence appears higher, the difference between intervention and control groups' abstinence would appear to decrease further into the postpartum period. There appears to be a kink in the pattern of abstinence amongst intervention participants, with a decline in abstinence at four weeks postpartum before increasing again at six weeks postpartum. This does appear to exist amongst control

[37] PR = Post randomisation;

participants, but not with such a large change, and the CIs overlap. Amongst control participants, the highest proportion abstinent occurs at three months postpartum, whilst among intervention participants this is at eight weeks postpartum. This suggests that cessation interventions during pregnancy may help prevent relapse earlier in the postpartum period. The proportion of participants reporting to be abstinent in both control and intervention groups decreases the more time elapses from the end of pregnancy. The same studies were used as in the primary analysis, and therefore only the pooled estimates of abstinence are reported here.

4.4.4.1 Four to eight weeks post randomisation

The proportion abstinent amongst controls was 0.113 (95% CI 0.047 to 0.179), while amongst interventions it was 0.187 (95% CI 0.131 to 0.244). The I^2 was high in both groups: 95% ($p<0.001$) in controls and 86.3% ($p<0.001$) in interventions.

4.4.4.2 End of pregnancy

In control participants, the proportion abstinent was 0.093 (95% CI 0.070 to 0.117), while in interventions it was 0.146 (95% CI 0.122 to 0.170). The I^2 in the control group was 94.1% ($p<0.001$), and the intervention group 88.1% ($p<0.001$).

4.4.4.3 Four weeks postpartum

Amongst control participants, the proportion abstinent was 0.018 (95% CI -0.019 to 0.054), whilst in intervention participants it was 0.050 (95% CI 0.034 to 0.066). The I^2 in the control group was 90.9% ($p=0.001$), and the intervention group 0% ($p=0.708$).

4.4.4.4 Six weeks postpartum

The proportion abstinent was 0.091 (95% CI 0.044 to 0.139) amongst controls, and 0.141 (95% CI 0.104 to 0.178) amongst interventions. The I^2 was higher amongst controls at 91.9% ($p<0.001$) compared to 79.6% ($p<0.001$) in interventions.

4.4.4.5 Eight weeks postpartum

Amongst intervention participants, the proportion abstinent was 0.177 (95% CI 0.142 to 0.212), while in controls it was 0.075 (95% CI 0.047 to 0.102). The I^2 was 7.2% (p=0.299) and 0% (p=0.498) respectively.

4.4.4.6 Three months postpartum

The proportion abstinent in intervention participants was 0.111 (95% CI 0.065 to 0.157), while in controls the abstinence was 0.099 (95% CI 0.047 to 0.152). The I^2 was 93.5% (p<0.001) in controls and 80.4% (p<0.001) in interventions.

4.4.4.7 Six months postpartum

Proportion abstinent was 0.069 (95% CI 0.039 to 0.098) for controls, and 0.091 (95% CI 0.058 to 0.123) for interventions. I^2 was 91.4% (p<0.001) for controls and 89.7% (p<0.001) for interventions.

4.4.4.8 12 months postpartum

Amongst control participants the proportion abstinent was 0.060 (95% CI 0.025 to 0.095), while in interventions it was 0.085 (95% CI 0.024 to 0.146). I^2 was 85.6% (p<0.001) for controls and 93.9% (p<0.001) for interventions.

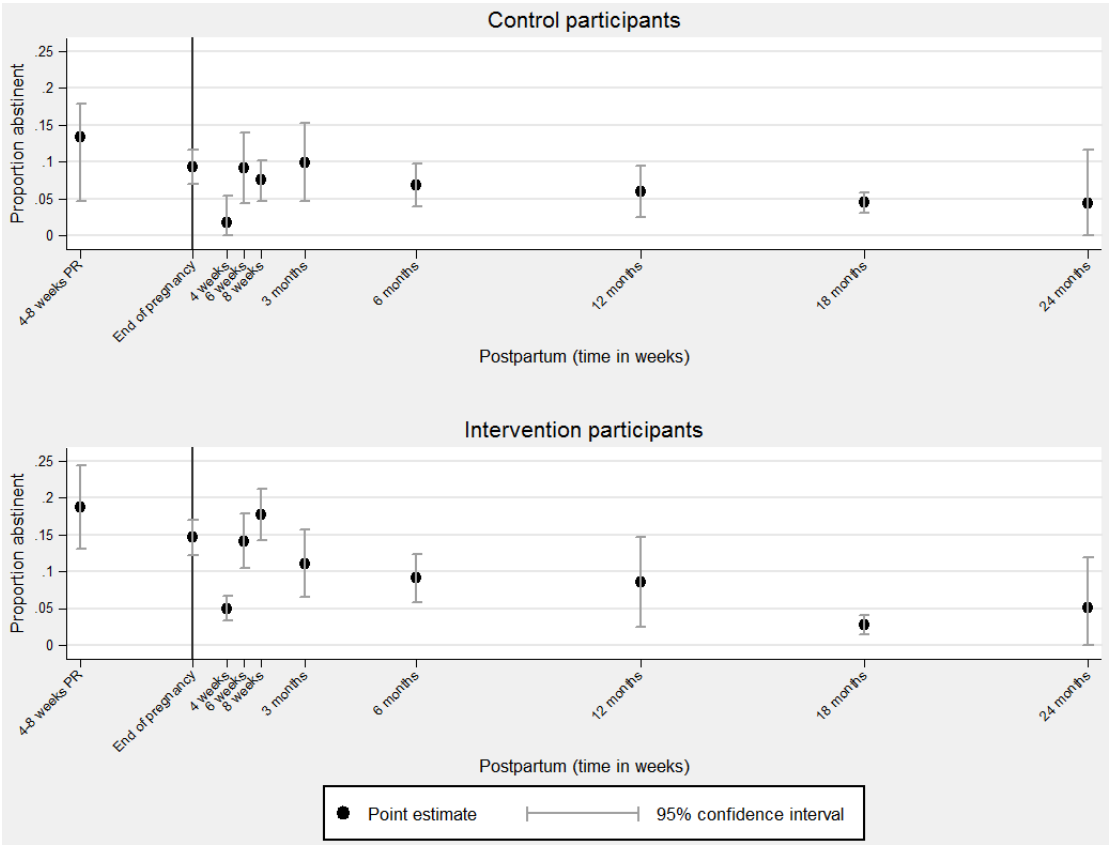
4.4.4.9 18 months postpartum

In intervention participants, the proportion abstinent was 0.027 (95% CI 0.014 to 0.041). In controls it was 0.045 (95% CI 0.031 to 0.058). I^2 was 0% (p=0.750) for controls and 0% (p=0.460) for interventions.

4.4.4.10 24 months postpartum

Proportion abstinent was 0.043 (95% CI -0.030 to 0.116) for controls and 0.051 (-0.017 to 0.119) for interventions. I^2 was 97.1% (p<0.001) for controls and 95.8% (p<0.001) for interventions.

Figure 4.5: Secondary analysis: Pooled estimates of abstinence of all participants split by control and abstinence groups, from the beginning of pregnancy[38]



4.4.5 Sensitivity analysis

To determine the potential impact on the meta-analysis findings of data quality, a sensitivity analysis was conducted involving only abstinence data that had been biochemically validated. This was available for four to eight weeks post randomisation, end of pregnancy, four, six, and eight weeks postpartum, three and six months postpartum. Appendix 12.6, Figure 12.4 outlines the results of this analysis, while Figure 4.6 displays the pattern of abstinence. At two time points, four to eight weeks post randomisation, and eight weeks postpartum, all the data was biochemically validated. However, at the other five time points, the primary analysis included both biochemically validated and self-reported abstinence. Comparing the biochemically validated abstinence with the abstinence estimated in the primary analysis, it can be seen that the abstinence rates for

[38] PR = Post randomisation

the biochemically validated data are lower. Although validated data were not available for beyond six months, Figure 4.6 demonstrates that the abstinence rates seem to be decreasing with time from the end of pregnancy. However, there appears to be a different pattern of behaviour at four, six, and eight weeks postpartum. After the end of pregnancy, abstinence seems to deteriorate at four weeks postpartum, before increasing again at both six and eight weeks postpartum. Consideration should be given that the four weeks postpartum abstinence is based on only one study, which could potentially be an outlier. Abstinence then starts declining at three and six months. Overlooking time points where only biochemically validated data was reported, the results of the sensitivity analysis are below.

4.4.5.1 End of pregnancy

21 studies reported biochemically validated abstinence. [123, 195, 202, 243, 245-255, 257-259, 262, 264, 265] The pooled abstinence was 0.120 (95% CI 0.100 to 0.139), and the I^2 was 92.2% ($p<0.001$).

4.4.5.2 Four weeks postpartum

One study reported biochemically validated abstinence. [262] The pooled abstinence was 0.047 (95% CI 0.035 to 0.062).

4.4.5.3 Six weeks postpartum

Four studies reported biochemically validated abstinence. [248, 257, 260, 265] The pooled abstinence was 0.093 (95% CI 0.054 to 0.133), and the I^2 was 85.2% ($p<0.001$).

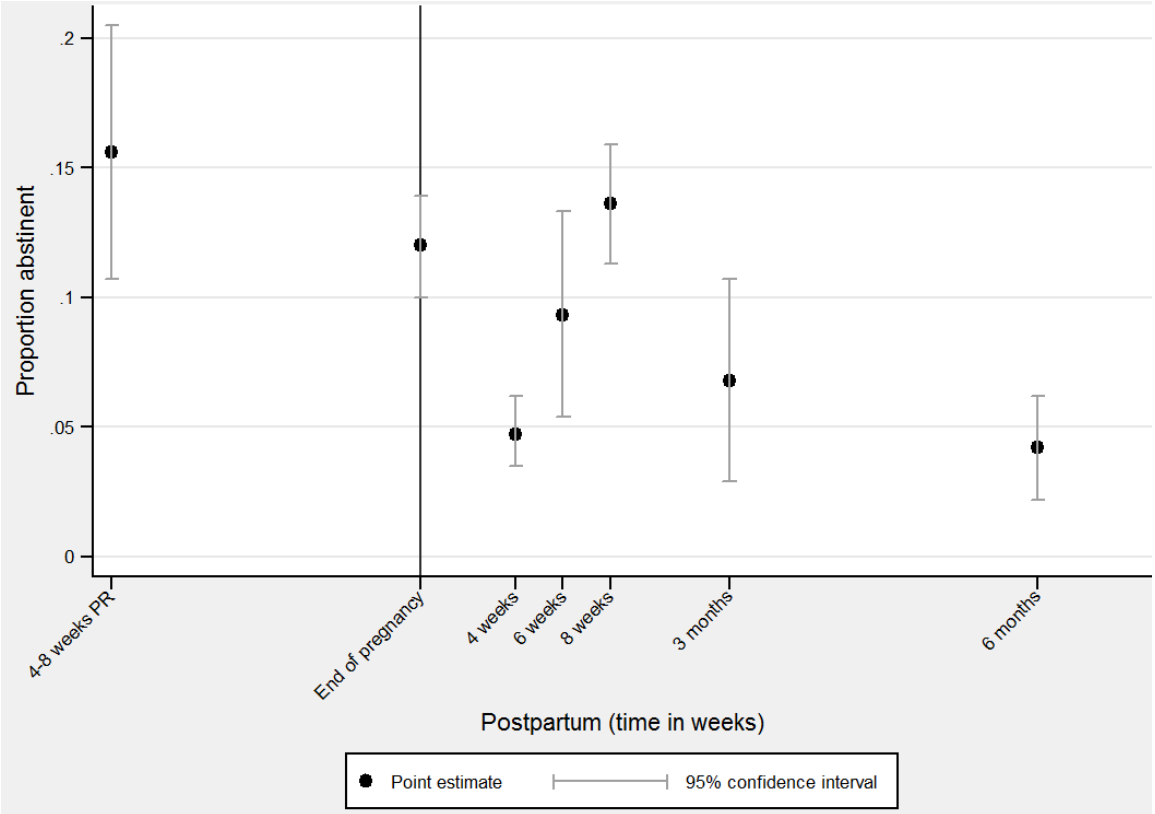
4.4.5.4 Three months postpartum

Three studies reported biochemically validated abstinence. [250, 251, 254] The pooled abstinence was 0.068 (95% CI 0.029 to 0.107), and the I^2 was 61.8% ($p=0.073$)

4.4.5.5 Six months postpartum

Five studies reported biochemically validated abstinence. [202, 245, 250, 252, 259] The pooled abstinence was 0.042 (0.022 to 0.062), and the I^2 was 73.0% ($p=0.005$)

Figure 4.6: Sensitivity analysis: Pooled estimates of abstinence of participants with biochemically validated abstinence, from the beginning of pregnancy[39]



4.5 Discussion

To the author's knowledge, this is the first time that a meta-analysis has been undertaken to derive pooled rates of abstinence from smoking in the postpartum period. The study demonstrates that by one year postpartum, only around 7% of trial participants remain abstinent, and that by two years postpartum this has declined to approximately 5% of participants. Most relapse seems to occur between three and six months postpartum, with abstinence only declining slightly beyond six months. However, the results at 18 and 24 months postpartum are only based upon two studies, which should be taken into consideration when interpreting these results. When considering abstinence in relation to receipt of cessation interventions, at most time points in the postpartum period, the proportion abstinent is higher amongst intervention than control participants; however, this difference almost disappears after 12 months postpartum. Furthermore, the CIs for

[39] PR = Post randomisation; PP = Postpartum

control and intervention groups overlap for all time points except for end of pregnancy and eight weeks postpartum. Overall, although cessation interventions appear to be effective at reducing smoking during pregnancy, effects diminish after pregnancy and this is an important public health issue.

4.5.1 Limitations of the review

There are several limitations to this study. This review has described the patterns of abstinence, rather than relapse curves, in the postpartum period; this was because the longitudinal abstinence data required were not available. A relapse curve consists of either a line plotted between several points demonstrating relapse to smoking amongst a cohort of quitters, or a survival curve using data on the exact day a quitter goes back to smoking. [266] However, in this review, our cohort includes both smokers and quitters at the end of pregnancy, and only uses seven-day point prevalence data to generate abstinence data at the pre-specified time points. This creates two problems. Firstly, we cannot calculate relapse rates because the individuals reporting abstinence in the postpartum period are not necessarily the same as those who reported abstinence at the end of pregnancy. Secondly, relapse can happen at any time, and since we only report seven-day point prevalence around certain points, participants could have started smoking and then quit again, without it being captured. Consequently, because of these limitations, we cannot calculate relapse rates and/or relapse curves based upon our pooled results. However, the use of point prevalence abstinence data as an estimate for relapse is an advance on previous estimates, which have been based upon expert opinion or studies in non-pregnant populations. [137, 139]

Not all included studies report data at every time point. Although there are 26 included studies in this review with 10,942 patients, for some time points there were relatively few studies which reported data. This suggests that at certain time points, the cohort of participants is restricted, which implies that the pooled estimate is not as precise as at others. Therefore, the results of the pooled estimates at the time points with few studies should be taken with caution. This could also potentially explain why the CIs on the proportions are generally quite wide, though heterogeneity amongst studies may also contribute.

There is a potential bias in the primary and secondary analyses because we include self-reported abstinence as well as biochemically validated abstinence. This is because studies which report the longer term outcomes, such as 12, 18 or 24 months, only report self-reported abstinence. There is evidence that self-reported abstinence is an inaccurate measure, with trial participants often reporting cessation, when in reality they are smoking, leading to a positive abstinence bias in the data. [267] To investigate this, we conducted a sensitivity analysis, where we restricted our meta-analysis to biochemically validated data only, which was only available up to the first six months postpartum. Although biochemically validated abstinence was consistently lower than the proportions estimated when including both types of data, there was no statistically significant difference in abstinence between the primary analysis and sensitivity analysis. This would suggest that although there may be slight bias caused by including self-reported data, it has little impact on the validity of our results and therefore we can conclude that self-reported data does not lead to any bias in the meta-analysis.

Across all the pooled estimates, the heterogeneity was very high, suggesting that the studies included in the review are potentially too different to be combined together. A potential cause is the pooling of studies employing different cessation interventions; it is expected that different interventions will have different abstinence rates and women enrolled to trials investigating a variety of interventions are likely to vary themselves. Consequently, it is possible that heterogeneity is caused by the included trials utilising very different populations of pregnant women, with unknown differences in characteristics. Another potential source for the heterogeneity is the combining of slightly different follow up points into one time point estimate. For example, for six months postpartum, pooled estimates were spread from 24 weeks postpartum to 26 weeks postpartum. To try and avoid this heterogeneity, we tried to group time points relatively close together; however, this trade-off was still made. Consideration to this high heterogeneity should be given when interpreting the results of this meta-analysis.

One final limitation is that there is potential evidence of publication bias occurring in our data, as suggested in the funnel plot Figure 4.3, which suggests that smaller studies with lower abstinence rates appear not to be published, and therefore this review could be missing data from these absent studies. It is unclear what impact including any missing studies would have on the results of this meta-analysis.

4.5.2 Strengths of the review

This review has several important strengths. For the first time, data from trials of smoking cessation interventions have been combined to demonstrate patterns of abstinence in the postpartum period. Consideration should be given that all the studies were trials, and trial participants could be deemed a 'special group' of the population, so the review may not be as representative as one including other studies such as cohort and cross-sectional. However, this meta-analysis uses a cohort of 10,942 women, making it by far the largest study in this area. With such a large number of participants, the results are a potentially accurate measure of abstinence after pregnancy, and more representative of the general population of smoking pregnant women than smaller studies.

Since the review only uses trial data, it could be considered that the review is using the best source of high quality data on smoking during and after pregnancy. Trial data is more likely to be collected consistently at a high standard, whereas cohort data has a greater tendency to have used routinely collected data of potentially lower standard. However, it is unsurprising that few trials report long term postpartum follow-up, either biochemically validated or self-reported, due to the high cost and workload of data collection, which can make it unpractical. Using routinely collected data would not only have increased the available studies for meta-analysing, it is also likely that the review would have been able to estimate relapse further than 24 months after pregnancy. However, routinely collected data is less likely to be have been biochemically verified, and more prone to bias than data collected by clinical trial. Therefore, it could be argued that the inclusion of cohort data would have introduced further bias into the meta-analysis, and hence potentially have degraded the quality of the review. Furthermore, cohort studies are more likely to include women who spontaneously quit rather than utilising a cessation intervention, which would generate relapse rates which were not relevant to women who access cessation interventions during pregnancy. Crucially, the data at the end of pregnancy was generally robustly assessed, giving an accurate measure of smoking behaviour as a baseline to estimate relapse in the postpartum period. This may not be so well-recorded in observational studies. This would imply that this review is using the most accurate data available to estimate postpartum abstinence.

4.5.3 The review in context of the limited longitudinal data on relapse in the postpartum period

Three studies included in the review report sustained abstinence at several time points in the postpartum period, but these data could not be meta-analysed because each study reported cessation at different time points. [123, 253, 262] Pollak et al estimated that by three months postpartum, 69% of women had relapsed. [253]. Lawrence et al estimated that at four weeks postpartum, relapse was 25%, and by 18 months postpartum, it was 88%. [262] and Cooper et al's data show relapse to be to be 45% at six months, 68% at 12 months, and 77% at 24 months. [123]

Comparing these relapse rates with the abstinence estimates estimated in this review is very difficult. One potential method is to assume that all those individuals reporting abstinence in the postpartum period are the same as those participants reporting abstinence at the end of pregnancy. This allows a relapse percentage at the time point to be calculated by dividing the abstinence estimate at a postpartum time point by the end of pregnancy estimate. Using this approach, relapse is estimated at 71% four weeks, 12% by three months, 35% by six months, 41% by 12 months, 71% by 18 months, and 63% by 24 months. Comparing these values with the longitudinal data estimates above suggests that our review estimates would appear to be conservatively estimating relapse in the postpartum period, except for four weeks postpartum where the review estimate is much higher. However, data at four weeks may be generated by 'outliers', since only two studies (Lawrence et al and Dunkley [244, 262]) report data at this time point, and both had lower end of pregnancy estimates for abstinence than the pooled estimate (pooled: 0.126, Dunkley: 0.040, Lawrence et al: 0.063). However, these relapse rates should be interpreted with great caution, because the assumptions outlined above may be unrealistic.

4.5.4 The review in context of the current literature on relapse in the postpartum period

The review findings seem to closely match what has been found in the literature. At six months postpartum, studies estimated that between 30% and 76% of women relapse to smoking. [217, 221, 223-231] For 12 months postpartum, the literature estimated that 32% to 59% of women relapsed [221, 227, 232, 233]. Studies investigating postpartum relapse after 12 months are relatively scarce, however Lemola et al estimated that 77% of women had relapsed by 18 months postpartum [234], and Martin et al estimated that 59% of women had relapsed by 24 months postpartum. [235] While the review supports the observational studies' estimates of relapse for 12 and 24 months postpartum, with proportion abstinent at both these time points being very low, there do appear to be some slight differences in postpartum relapse behaviour. The observational studies suggest that there is a large drop in abstinence relatively quickly after pregnancy, within three months postpartum. The pooled estimates in this review do suggest that there is a decline in abstinence by three months postpartum; however, not to the same degree as in the cohort studies.

The difficulty in comparing the observational studies with the review can be seen by contrasting the postpartum estimates from the review with the results by Rattan et al. The study estimated that amongst women who had stopped smoking during pregnancy, 44% had relapsed by five years postpartum, 36% at 14 years after childbirth, and 36% at 21 years after childbirth. [230] However, Rattan was a observational study collecting self-reported seven-day point prevalence estimates, which is potentially open to reporting bias if women chose not to report their actual smoking status. Furthermore, the study included women who were spontaneous quitters as there was no cessation intervention, implying a different population to the review. Many of the aforementioned cohort studies include women who had either stopped smoking before, or had quit very early in, pregnancy. [217, 221, 223, 224, 227, 228, 231] The review includes women who are potentially more reliant on smoking, which could explain why the prevalence of smoking after pregnancy appears to be higher in this review compared to the literature. However, all the women included in this review will have received some form of cessation intervention, which could be very useful for predicting the impact of such interventions during pregnancy on the smoking

behaviour of women after pregnancy. This would be very useful for predicting the relapse rates of new cessation interventions.

4.5.5 The review in context of the current literature of economic models of smoking cessation during pregnancy

Four economic models have incorporated postpartum smoking behaviour. Mallender et al did not incorporate a relapse rate but assumed that 2% of smokers would quit permanently each year [190], so a comparison cannot be drawn. Tappin et al assumed relapse rates of 60% and 30% at three months postpartum for the intervention and control groups respectively [196], before applying long-term estimates from studies on non-pregnant populations. In this review, the corresponding values at three months postpartum were 0% and 24%. Taylor estimated that 70% of women had relapsed at 12 months postpartum [139], while Ruger et al estimated 35% relapse over the remaining lifetime[137], whereas the corresponding figure from this review is 59%. The estimate used by Taylor was based upon expert opinion, which may be considered inaccurate as it could be heavily prone to bias, although it seems to closely match the one year relapse rate as estimated by Cooper et al. [123] Ruger's estimate came from a recommendation in the 1990 US Surgeon General's report, which is not from a pregnant population. [138] Assuming that this review gives more accurate estimates of relapse, both Tappin et al and Taylor seem to slightly overestimate the number of women relapsing in the postpartum period, while Ruger et al is difficult to compare as it is from a non-pregnant population over an entire lifetime. This review suggests that 35% may be too low, but as it only looks at up to two years postpartum, what happens beyond that is unknown.

4.5.6 Changes in smoking behaviour over the postpartum period

This review not only highlights that postpartum rates of abstinence are lower than is currently perceived in the literature, but also highlights potential changes in the smoking behaviour of the mother in the postpartum period. Abstinence appears to be fairly consistent up to eight weeks postpartum, before declining; the two biggest drops in abstinence occur between three and six months postpartum and 12 and 18 months postpartum. Although we have no information on the reasons why the abstinence rates

dropped at these points, it may be possible that a new mother may choose to relapse to smoking as a method of coping with stress caused by the new child. Smoking is known to be a method of stress-relief and therefore it could potentially be used by the mother to help control for the stress associated with the new child. [218] An alternative possibility is that women have not actually relapsed, however they do not respond to the trial's request at these time points. This means that in the intention to treat analysis they are counted as relapsed, which could be an incorrect assumption. Although there is some evidence of high attrition in some studies, we cannot quantify how much of an impact this has on our abstinence rates.

Of interest is that the highest pooled rates of abstinence in the postpartum period were at eight weeks postpartum. These were even higher than at the end of pregnancy, which suggests that relapse to smoking after pregnancy may not be a continuous decline like it appears to be following quit attempts made by non-pregnant smokers. [268] One possible explanation for this is that mothers who did not report cessation at the end of pregnancy are now making a quit attempt because they are trying to do the best for the health of their new child.

A similar explanation could be used for understanding why there is a big drop in abstinence at four weeks postpartum and subsequent increase at six weeks postpartum. At four weeks postpartum, we could have mothers who have relapsed to smoking because they are no longer pregnant; conversely, by six weeks they may have resumed cessation because they realise that their smoking could impact on the infant. However, the abstinence estimates at four weeks are based on two studies [244, 262], which have lower rates of abstinence compared to other included trials, and therefore may be outliers, hence we cannot draw any conclusions as to whether there is a change in smoking behaviour between end of pregnancy and four weeks, and between four and six weeks postpartum.

4.5.7 Comparing the smoking behaviour in the postpartum period with that of general smoking cessation interventions

Compared to more general smoking populations, there are clear differences in relapse behaviour between pregnant and non-pregnant populations. Coleman et al conducted a systematic review of pharmacotherapic interventions linked with NHS Stop Smoking services. [268] 16 studies were included, with 8,679 participants, and interventions

consisted of behavioural support as well as NRT, bupropion and varenicline. The pooled estimates of abstinence were 49% (95% CI, 42-56%) at the end of one month, 44% (95% CI, 40-48%) at three months, 31% (95% CI, 28-33%) at six months and 26% (95% CI, 23-29%) at 12 months post-randomisation. These are much higher than our review, suggesting that a pregnant woman is more likely to relapse even though she has received an intervention. This implies that the use of general smoking population data for modelling postpartum relapse is incorrect and therefore it would seem more appropriate to use the results generated in this review in any improved economic model.

Hughes et al investigated relapse amongst self-quitters in another systematic review. [266] A narrative synthesis was adopted due to the significant amounts of heterogeneity encountered. From the seven included studies, abstinence at the end of one month post-quit date was between 15 and 28%, 10 - 20% by three months, 3 - 5% between six and 12 months. The authors concluded that most relapse occurred within eight days of quitting. In this review, abstinence rate at three months were relatively similar to the abstinence rates at the end of pregnancy, suggesting there was no such rapid drop. However, after three months the proportions abstinent in our review become very similar to the result found by Hughes et al. On the other hand, in this review all mothers were exposed to an intervention, whereas in the review by Hughes et al there was no cessation intervention. This might explain the apparent differences in relapse behaviour.

4.6 **Summary**

This review demonstrates that, excluding the four week post randomisation estimate, relapse appears to steadily increase over the postpartum period. The highest estimate for abstinence occurs at eight weeks postpartum, with around 14% of women reporting abstinence. Although there seemed to be some evidence of behaviour changes in the first few weeks postpartum, up till eight weeks postpartum abstinence seemed relatively steady. However, after three months postpartum, the relapse rates increased such that by 12 months postpartum only 7% of women reported abstinence, declining to 5% at 24 months. Although the review found evidence that the proportion of women in the intervention groups who relapsed were lower, the 95% CIs for control and intervention groups crossed, suggesting that there was no significant difference in relapse between the two groups. With so few people abstinent, smoking postpartum is an important health

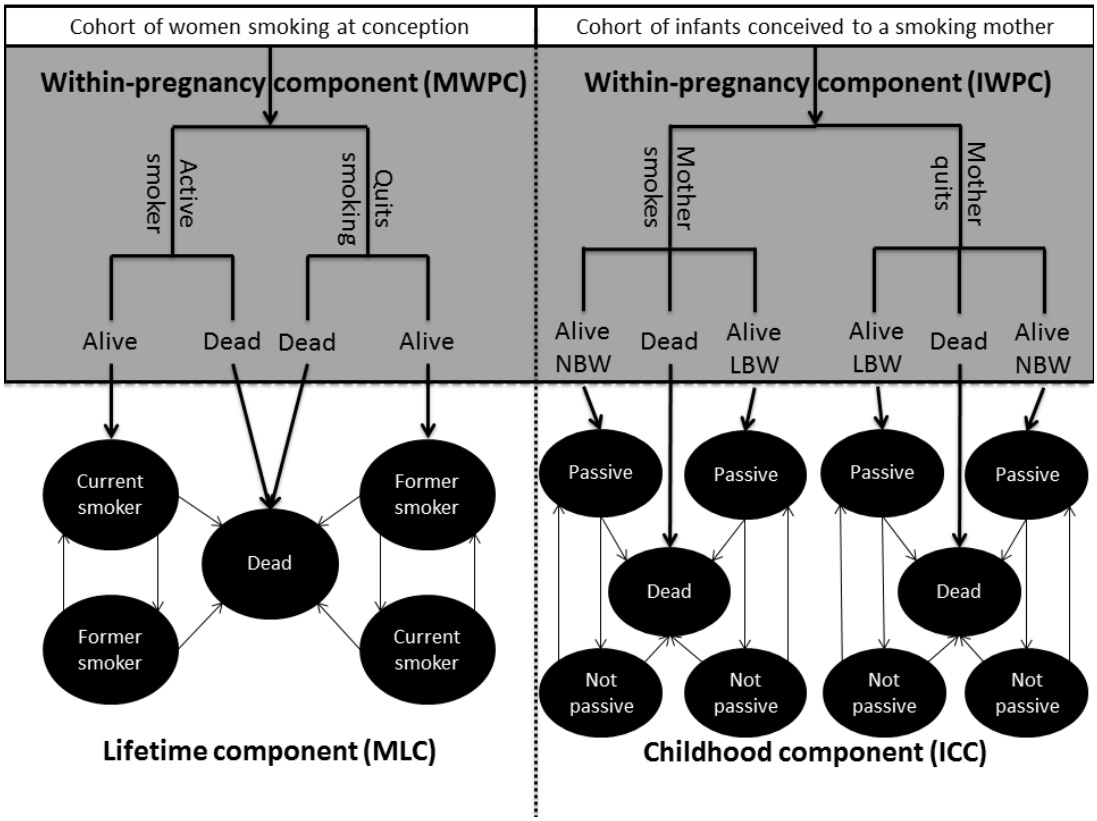
issue that requires addressing, especially considering the health impacts of passive smoking. This review also highlights the poor quality of the trials that report data postpartum. To generate better estimates of postpartum abstinence, higher quality studies investigating postpartum smoking using biochemically validated abstinence, either using a clinical trial design or a high quality observational study on women who have received a cessation intervention, are required. However, a VOI analysis should be conducted to determine whether there is a requirement to investigate this further, as these studies are likely to be expensive, and may not yield a benefit in terms of information gained.

Chapter 5: The ESIP model: Description of the maternal-foetal 'within-pregnancy' component

5.1 Introduction

Previous chapters of this thesis have discussed the preceding literature around the economic impacts of smoking cessation during pregnancy, as well as critiquing the previously-derived models' structures and gaps. Focus now shifts to describing the Economic impacts of Smoking In Pregnancy (ESIP) model. ESIP is formed of four standalone economic models which are referred to as 'components'. The following chapters will describe each of the four component models which are brought together to form ESIP. Figure 5.1 gives a simplified structure of the complete ESIP model.

Figure 5.1: Simplified overall ESIP model structure



This chapter introduces and describes the first two component models, represented by the grey area in Figure 5.1. The components described in this chapter are the Maternal 'Within-

Pregnancy' Component (MWPC) and the Infant 'Within-Pregnancy' Component (IWPC). These run simultaneously, focusing on the impacts of smoking and smoking cessation on materno-foetal delivery complications and birth outcomes within the time frame of pregnancy. Later chapters outline the Mother's Lifetime Component (MLC) and Infant Childhood component (ICC), which capture the impacts of smoking during pregnancy on the health of the mother and infant after pregnancy.

5.2 **Objectives**

5.2.1 Primary objective:

To describe the 'within-pregnancy' components for mother and infant as part of the ESIP model.

5.2.2 Secondary objectives:

1) Outline and describe the rationale of the structure of the MWPC and the IWPC
2) Identify relevant parameters and describe how these fit together within the MWPC and IWPC
3) Describe the link between the MWPC and IWPC and its function
4) Identify relevant QALYs contingent on smoking status, apply appropriate decrements for complications, and fit these within the MWPC component
5) Identify relevant costs for maternal pregnancy complications, and fit these to the MWPC
6) Identify relevant costs for infant birth outcomes , and incorporate in the IWPC

5.3 **Overview of model structure**

5.3.1 Justification for type of model

A decision tree structure was chosen for the within-pregnancy components. For a discussion of modelling approaches, please see section 1.6.7. There were three reasons for this choice of approach:

1) Pregnancy is a short time horizon, typically nine months or less. Therefore, since the time horizon was less than one year, discounting need not apply, and hence models which allow the introduction of time dependence did not seem to have any advantages in this setting
2) We were assuming that the end of pregnancy was time zero in the lifetime models (discussed in Chapters 6 and 7), therefore that all events within-pregnancy were happening simultaneously
3) All the decision trees were likely to be bushy, and consideration was given to alternative approaches. However, for a Markov model or other modelling approach to capture the same impacts and information, it was likely that they too would be very complicated with multiple states, and hence the decision tree was chosen as the simplest form to undertake this analysis

5.3.2 Maternal model structure

The model assumes that all women who enter the model are smokers at conception who can either remain as smokers throughout pregnancy or quit before pregnancy ends; women who stop smoking temporarily in pregnancy are assumed to be part of the 'smoke throughout pregnancy' arm of the decision tree. The initial phase of the model is given in Figure 5.2.

Figure 5.2: Initial phase of decision tree structure for the mother

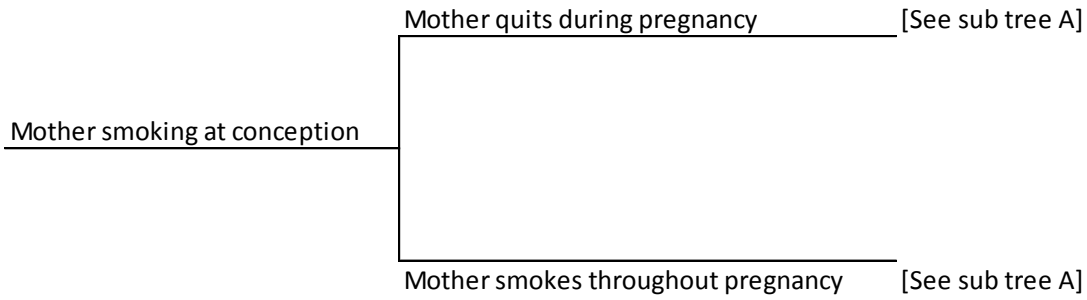
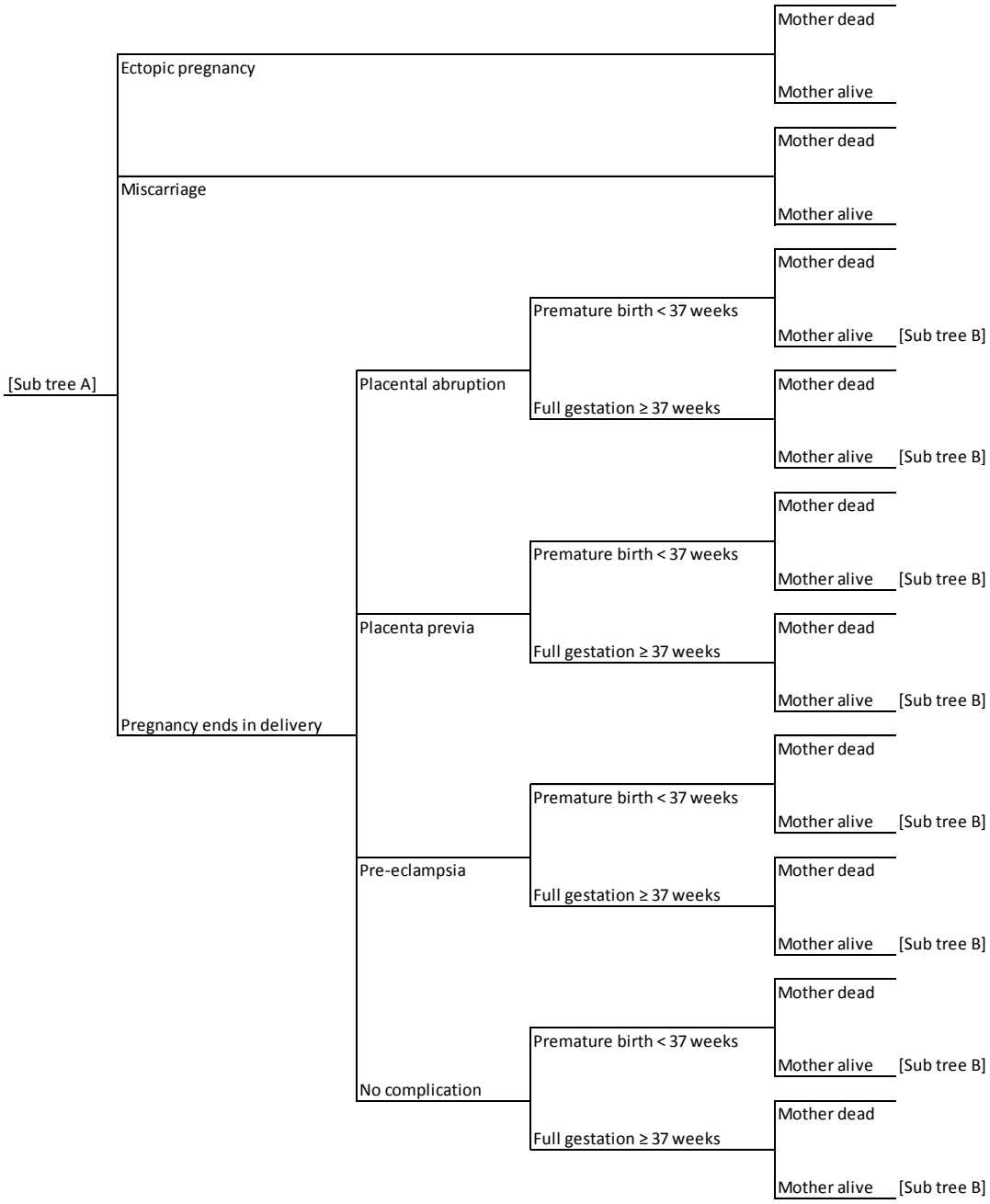


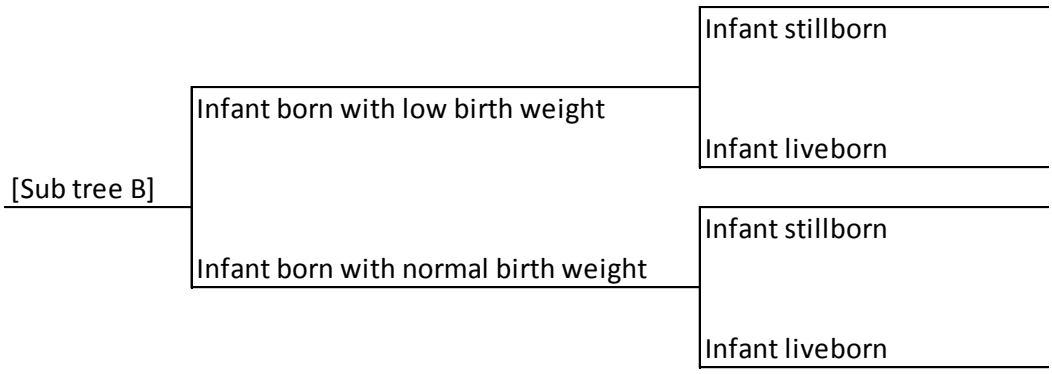
Figure 5.3 illustrates the next part of the model structure, for smokers (Sub tree A); there is a similar sub tree for women who stop smoking in pregnancy. For both groups of women (quitters and smokers), the model then estimates numbers of women who suffer from an ectopic pregnancy or miscarriage. For pregnancies which ended in a delivery, the mother can deliver with or without a complication, and can be premature or full-term. Finally, the model then distinguishes those women who survive and those who die.

Figure 5.3: Determining premature birth and mother's survival of pregnancy [Sub tree A]



The final stages of the maternal model determine the frequency of stillbirths and LBW. The structure for this part of the decision tree is given in Figure 5.4.

Figure 5.4: Maternal: infant decision tree linkage to determining infant birth outcomes [Sub tree B]



The reasons for adapting these structures for the MWPC are:

1. As ectopic pregnancies and miscarriages occur early in pregnancy, it is necessary to determine the number of mothers who suffer these outcomes early in the model.
2. The pregnancy complications included in the maternal decision tree are associated with higher risks of premature birth. The length of gestation is important as it could impact on healthcare costs; for example a reduced cost of antenatal care due to fewer midwife visits. The model determines whether or not the woman survives pregnancy before determining infant birth outcomes.
3. To capture maternal impacts of stillbirth and other adverse foetal outcomes, the model determines the number of infants born to living mothers who suffer these complications. An increase in the risk of stillbirth can be attributed to both small for gestational age and premature birth. [269-271] Although small for gestational age is not included in the MWPC, such infants are most likely born LBW, since the definition is infants born with weight below the 10^{th} percentile for gestational age. To incorporate these associations, the MWPC determines whether the birth is premature and/or LBW before determining if stillbirth occurs, hence stillbirth and live birth are the last branches of the decision tree.

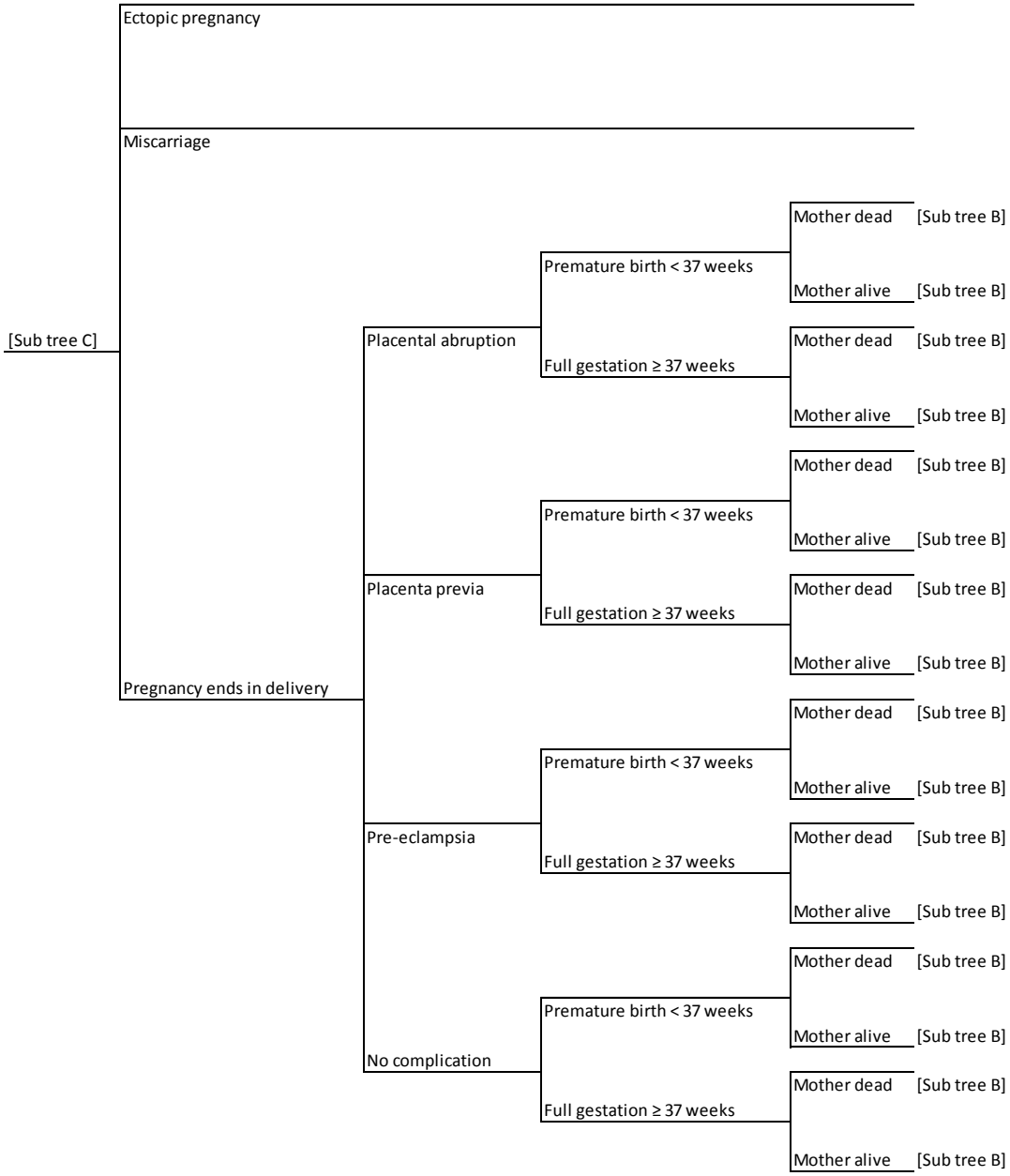
5.3.3 Infant model structure

The IWPC estimates the impacts of the maternal complications on the birth outcomes for the infant. The model assumes that all singleton infants are conceived to a smoking mother, and are matched to the women included in the MWPC. To achieve the match between the infants with the women, the IWPC seen in Figure 5.5 has an almost identical structure to the MWPC. The differences between the MWPC and IWPC are:

1. The removal of the arms relating to the mother's survival for the ectopic pregnancy and miscarriage branches, as the IWPC assumes that all infants who suffer either of these conditions die.
2. The addition of the birth weight and stillbirth branches (sub tree B, see Figure 5.4) after the 'mother dead' arm, since the infant can still be born alive following maternal death.

Infants are conceived to a smoking mother as per Figure 5.2, but rather than progress to 'Sub tree A', they progress to 'Sub tree C' shown in Figure 5.5 below. Once they have progressed through 'Sub tree C', they flow through 'Sub tree B' in Figure 5.4 to determine their birth weight and birth status. As the structures are almost identical, the parameters used in the MWPC are replicated in the IWPC. The structures for both the maternal model and infant models together are given in full in Appendix 12.9, Figure 12.5, Figure 12.6 and Figure 12.7.

Figure 5.5: Initial structure of infant decision tree: foetal loss and prematurity [equivalent to Sub tree A in Figure 5.3]



5.3.4 Note on included morbidities in the within-pregnancy components

Chapter 2 identified nine conditions which have a strong association with smoking during pregnancy which arguably warrant inclusion in the within-pregnancy components. However, the MWPC and IWPC only include seven morbidities, with PROM / PPROM and congenital anomalies excluded. Congenital anomalies appear to be exceedingly rare, and the impact varied upon the type of abnormality developed. Therefore, because of the rarity of the condition, they were excluded.

There was also strong evidence for a causal link between maternal smoking and PROM, but this was not included in the components because the NHS Maternity Statistics for England data did not report the number of occurrences by gestation length except for the year 2012-2013, so it was not possible to differentiate between PROM and PPROM in most of the data. [150, 272] Furthermore, while PPROM appeared to have a strong association [2], no evidence could be identified for parameterising full gestation PROM.

5.4 Deriving probability parameters to populate model

5.4.1 Foetal loss before delivery

It was necessary to estimate the number of pregnancies with foetal loss (FL) that did not require a delivery episode. FL was estimated using Hospital Episode Statistics for England (HES) NHS Maternity data, covering the years 2006 to 2013. [272] These data report the number of ectopic pregnancies and miscarriages requiring a hospital stay. Although some occurrences of these conditions do not require a hospital stay and hence are not included in these statistics, HES data provides the best available estimates for occurrence rates for smoking and non-smoking women. The numbers of occurrences are given in Table 5.1.

Table 5.1: Number of all pregnancies that did not end in delivery (foetal loss)[40]

Year	Delivery episodes	Ectopic pregnancy episodes	Miscarriage episodes
2006-2007	629,207	9,941	43,155
2007-2008	649,837	10,352	43,870
2008-2009	652,638	10,348	43,390
2009-2010	652,377	10,635	45,232
2010-2011	668,195	11,157	43,005
2011-2012	668,936	11,294	42,538
2012-2013	671,255	11,199	39,800
Total	**4,592,445**	**74,926**	**300,990**
Probability of occurrence*		0.0151	0.0606

Source: Table 1.i HES NHS Maternity Statistics 2012-2013 **[150]**

* Miscarriage and ectopic pregnancies do not count as delivery episode, so the denominator is the sum of the number of deliveries, miscarriages, and ectopic pregnancies.

5.4.2 Complications of delivery

The mother could face three delivery complications: placental abruption; placenta previa; and pre-eclampsia. The frequencies with which these complications occurred were taken from HES NHS Maternity Statistics for England 2006-2007 to 2012-2013, details of which are given in Table 5.2.

[40] Includes smoking and non-smoking women

Table 5.2: Number of all pregnancies that had a delivery complication[41]

Year	Placental abruption episodes	Placenta previa episodes	Pre-eclampsia episodes	Deliveries with no complication*
2006-2007†	2,183	3,540	11,119	612,365
2007-2008†	2,375	3,758	11,718	631,986
2008-2009†	2,422	3,985	12,120	634,111
2009-2010†	2,506	4,093	12,778	633,000
2010-2011†	2,458	4,368	13,017	648,352
2011-2012†	2,491	4,446	12,598	649,401
2012-2013‡	2,666	4,420	13,211	650,958
Total	**17,101**	**28,610**	**86,151**	**4,460,173**
Probability of occurrence	0.0037	0.0062	0.0188	0.9712

* Number of delivery episodes (Table 5.1) minus deliveries with complications

† Source: Table 22 NHS Maternity Statistics (relevant year) **[273-278]**

‡ Source: Table 7.d NHS Maternity Statistics 2012-13 **[150]**

5.4.3 Deriving smoking status-contingent probabilities for experiencing included conditions

To derive the probability of a mother developing one of the five included conditions contingent on her smoking status by the end of pregnancy, the probability of occurrences in all pregnant women (i.e. smoking and non-smoking) was adjusted to allow for the impact of smoking. We assumed that delivery complications and FL events were mutually exclusive events and were therefore treated as independent of each other. Chapter 2 identified two meta-analyses which estimated the impact of smoking during pregnancy on the risks of developing each of these conditions. The relevant information is reproduced in Table 5.3.

[41] Includes smoking and non-smoking women

Table 5.3: Impact of smoking in pregnancy on the risk of developing included conditions

Condition	Pooled odds ratio	95% confidence interval (CI)	Source
Ectopic pregnancy	1.77	1.31-2.22	Castles 1999 [2]
Miscarriage	1.32	1.18-1.48	DiFranza 1995 [3]
Placental abruption	1.62	1.46-1.77	Castles 1999 [2]
Placenta previa	1.58	1.04-2.12	Castles 1999 [2]
Pre-eclampsia	0.51	0.38-0.64	Castles 1999 [2]

We assumed that women either smoked throughout pregnancy or stopped successfully during pregnancy. Those who smoked throughout included those who did not make a quit attempt and those with temporary periods of abstinence (relapsed by the end of pregnancy), and were assigned the risks associated with smokers. Abstinent women included all those who had successfully quit by the end of pregnancy, including those who had ceased very close to the end of their pregnancy, and were assigned the risks associated with never smokers. This was necessary because there were no available data on the relationship between timing of quitting and risk of conditions, and can be seen as a conservative assumption as the benefits from temporary abstinence are not claimed.

To calculate the difference in probabilities, the method outlined by Flack et al for attributing the increase prevalence of diseases amongst smokers was adapted. [129] The following equation was used:

$$\boldsymbol{A} = (\boldsymbol{P_S} \times \boldsymbol{B}) + (\boldsymbol{P_{NS}} \times \boldsymbol{C}) \quad (5.1)$$

Where $\boldsymbol{A}$ is the odds of the condition in all women (i.e. smokers and non-smokers), $\boldsymbol{P_S}$ is the prevalence of smoking throughout pregnancy, $\boldsymbol{B}$ is the odds of the condition occurring in smokers, $\boldsymbol{P_{NS}}$ is the prevalence of non-smoking during pregnancy (both quitters and never smokers), and $\boldsymbol{C}$ is the odds of the condition occurring in non-smokers.

The odds B can also be expressed as:

$$B = C \times OR_S \tag{5.2}$$

Where OR_S is the odds ratio for occurrence in smokers versus non-smokers.

Replacing this in equation (5.1) gives:

$$A = (P_S \times C \times OR_S) + (P_{NS} \times C) \tag{5.3}$$

Rearranging for C gives the equation:

$$C = \frac{A}{(P_S \times OR_S) + P_{NS}} \tag{5.4}$$

This equation allows the odds C to be calculated. The odds B can then be calculated using equation (5.2).

5.4.4 Worked example for ectopic pregnancy

To demonstrate, the calculation of the probability of ectopic pregnancy contingent on smoking status is given as a worked example. The odds for all pregnant women, regardless of smoking status, for developing ectopic pregnancy are:

$$Odds\ (ectopic\ pregnancy|all\ pregnant\ women) = \frac{p_o}{1 - p_o} = \frac{0.0151}{1 - 0.0151} = 0.0153$$

Where p_o is the probability of ectopic pregnancy in all women (smokers and non-smokers) (see Table 5.1).

From the latest IFS, it was estimated that 12% of women smoke throughout pregnancy, while 88% are either never smokers or stopped smoking before or during pregnancy (i.e. were abstinent by the end of pregnancy). [135]

From Castles et al, the odds ratio for smokers developing ectopic pregnancy was 1.77. [2] Substituting into equation (5.4) gives the odds for a non-smoker:

$$C = \frac{0.0153}{(0.12 \times 1.77) + 0.88} = 0.0140$$

Using (5.2), the odds for a smoker developing ectopic pregnancy are:

$$B = 0.0140 \times 1.77 = 0.0248$$

The probabilities for ectopic pregnancy contingent on smoking status (p_s is the probability of ectopic pregnancy amongst smoking women, and p_{ns} is the probability of ectopic pregnancy amongst non-smoking women) can then be calculated by transforming the odds:

$$p_s = \frac{odds(ectopic\ pregnancy|smoker)}{1 + odds(ectopic\ pregnancy|smoker)} = \frac{0.0248}{1 + 0.0248} = 0.0242$$

$$p_{ns} = \frac{odds(ectopic\ pregnancy|non\text{-}smoker)}{1 + odds(ectopic\ pregnancy|non\text{-}smoker)} = \frac{0.0140}{1 + 0.0140} = 0.0138$$

This process was repeated for all conditions, the results of which are given in Table 5.4 and Table 5.5.

Table 5.4 Probabilities of pregnancy not ending in delivery (foetal loss) contingent on mother's smoking status

Condition	Non-smoker	Smoker
Ectopic pregnancy	0.0138	0.0242
Miscarriage	0.0585	0.0758
Ends in delivery	0.9277	0.9000

Table 5.5: Probabilities of developing a pregnancy complication, contingent on smoking status

Condition	Non-smoker	Smoker
Placental abruption	0.0035	0.0056
Placenta previa	0.0058	0.0092
Pre-eclampsia	0.0200	0.0103
No complication	0.9707	0.9749

5.4.5 Premature birth

The pregnancy complications included in the model (Table 5.5) are associated with increased premature birth, and to estimate prematurity associated with each, frequency data by length of gestation was sought. This is presented in Table 5.6.

Table 5.6: Number and risk of premature birth by complication

Condition	Total complication episodes	Premature episodes	Risk
Placental abruption	2,666	1,074	0.4029
Placenta previa	4,420	1,163	0.2631
Pre-eclampsia	13,211	3,618	0.2739
No complication	650,658	40,787	0.0627
Source: Table 7.d NHS Maternity Statistics for England 2012-13 **[150]**			

Shah et al estimated that smoking during pregnancy increased the risks of premature birth, with an odds ratio of 1.27 (95% CI 1.21 to 1.33). [67] It was assumed that smoking during pregnancy increased the risk of any premature birth across all complications. Using the same method as described earlier, the corresponding probability of premature birth contingent on smoking status was calculated for each complication as well as for pregnancies in which no complication was suffered; estimates are given in Table 5.7.

Table 5.7: Probability of premature birth within pregnancy morbidities and contingent on smoking status

Condition	Non-smoker	Smoker
Placental abruption	0.3952	0.4535
Placenta previa	0.2570	0.3052
Pre-eclampsia	0.2676	0.3169
No complication	0.0608	0.0760

5.4.6 Risk of maternal mortality

To estimate the impact of maternal mortality for the model, ONS mortality statistics for England and Wales were used; from these, numbers of women with live births (including singleton and multiple pregnancies) and maternal deaths in pregnancy for 2003 to 2012 were identified (Table 5.8).

Table 5.8: Number of deaths during pregnancy from ONS mortality statistics

Year	Number of women giving birth	Deaths during pregnancy	Deaths from ectopic pregnancy	Deaths from miscarriage	Deaths from abruption	Deaths from previa	Deaths from pre-eclampsia	Other deaths during pregnancy
2012*	721,574	46	0	0	1	0	4	41
2011*	716,040	44	0	1	2	0	0	41
2010*	715,467	35	1	0	0	0	2	32
2009*	698,324	63	1	0	1	0	5	56
2008*	701,297	44	3	2	0	0	3	36
2007*	682,999	47	2	2	0	0	2	41
2006*	662,915	41	2	0	1	1	4	33
2005†	639,627	36	2	1	1	0	6	26
2004†	633,728	46	3	1	0	0	3	39
2003†	615,787	45	3	0	2	0	3	37
Total	**6,787,758**	**447**	**17**	**7**	**8**	**1**	**32**	**382**

* Source: Table 5.15, Mortality Statistics: Deaths registered in England and Wales (Series DR) **[279]**

† Source: Table 2.15, Mortality Statistics: Cause, England and Wales (Series DH2) **[280]**

ONS estimates do not report the number of women giving birth that suffer complications; to estimate this, the 'all pregnancy' probabilities for conditions as reported in Table 5.1 and

Table 5.2 were multiplied by the total number of women giving birth. This derived an estimate of the total annual number of women suffering from one of the conditions to be included in the model. The mortality probability for each condition was then determined by dividing the actual number of deaths from that condition by the estimated number of maternities which suffered from it. As no literature was identified that suggested an increased mortality during pregnancy linked with smoking, it was assumed that smoking had no impact on maternal mortality in the presence of related conditions. Table 5.9 reports mortality probabilities used.

Table 5.9: Estimated number of conditions occurring and mortality risks during pregnancy

Condition	Death episodes	Derived occurrence episodes	Risk of death
Ectopic pregnancy	17	113,245*	0.00015*
Miscarriage	7	402,459*	0.00002*
Placental abruption	8	26,959	0.00030
Placenta previa	1	44,695	0.00002
Pre-eclampsia	32	133,590	0.00024
No complication mortality	382	6,582,514	0.00006
* ONS data excludes women who suffer from a miscarriage or ectopic pregnancy. This was estimated by multiplying the number of maternities by the ratio of total number of miscarriages, ectopic pregnancies, and delivery episodes over delivery episodes: 6,787,758 x (4,968,361/4,592,445)			

5.4.7 Impacts of prematurity on infant birth weight and stillbirth

An infant's birth weight is heavily reliant on gestation at birth [281, 282], and stillbirth is associated with both prematurity and birth weight. [271] Data reporting: i) birth weight by gestation and ii) stillbirths by birth weight and gestation for the years 2006 to 2011 were taken from ONS Child Mortality Statistics and ONS Gestation-specific Infant Mortality in England and Wales. [283, 284] Table 5.10 reports the number of stillbirths and live births by birth weight and prematurity. Prematurity was defined as birth occurring before 37 weeks gestation, and LBW was defined as an infant born weighing less than 2500 grams.

Table 5.10: Number of live births and stillbirths by birth weight and prematurity

Year	Premature LBW		Premature normal birth weight (NBW)		Full gestation LBW		Full gestation NBW	
	Live births*	Stillbirths †	Live births*	Stillbirths †	Live births*	Stillbirths †	Live births*	Stillbirths †
2011	30,837	2,158	19,857	141	19,850	356	649,080	1,156
2010	30,097	2,092	19,903	131	20,148	386	648,437	1,105
2009	30,668	2,120	19,720	140	20,090	351	6235,332	1,077
2007-2008	61,172	4,063	38,260	260	39,598	676	1,258,343	2,216
2006	31,516	2,097	18,812	156	18,608	326	600,529	1,023
Total	**184,290**	**12,530**	**116,552**	**828**	**118,294**	**2,095**	**3,791,721**	**6,577**

* Source: Tables 2/3 Gestation-specific infant mortality in England and Wales (relevant year) **[176, 285-288]**

† Source: Table 9 Child Mortality Statistics (years 2008 – 2011) **[289-292]**, Table 13 Mortality Statistics: Childhood, infant and perinatal, England and Wales (2006-2007) **[293, 294]**

Note: 2007-2008 gestation specific data was aggregated

Note: Although the gestation specific data defines prematurity as occurring before 37 weeks gestation, premature stillbirths are defined as occurring before 36 weeks gestation. This has been changed in the 2012 edition; however gestation-specific data is not yet available.

DiFranza et al determined that the relative risk for LBW and stillbirth for smoking in pregnancy were 1.82 (95% CI 1.67 to 1.97) and 1.26 (95%CI 1.19 to 1.34) respectively. [3] The model assumes that smoking during pregnancy increases the risks of LBW and stillbirth for both prematurely born and full gestation infants. The impact of smoking on the probabilities of an infant being born with LBW and/or stillborn were incorporated using the methods outlined in the previous section around incorporating conditions relating to pregnancy complications; the probabilities are given in Table 5.11 and Table 5.12.

Table 5.11: Probability of LBW conditional on smoking status and gestation

Gestation length	Non-smoker	Smoker
Premature <37 weeks	0.5703	1.0000
Full gestation ≥37 weeks	0.0280	0.0509

Table 5.12: Probability of a stillbirth conditional on birth weight, gestation, and smoking status

Birth weight/Gestation length	Non-smoker)	Smoker)
LBW/premature	0.0617	0.0778
NBW/premature	0.0068	0.0086
LBW/ full gestation	0.0169	0.0213
NBW/ full gestation	0.0017	0.0021

5.5 Estimating maternal health related quality of life parameters for inclusion in model

To estimate the health-related impacts of smoking and smoking cessation during pregnancy required the calculation of QALYs. To determine the impact of smoking and quitting on the health of the mother, along with any health loss associated with suffering from one of the included conditions, utility values were required to weight the life year during pregnancy.

Utility values for currently smoking and former smoking women were calculated using the utility tariff described by Maheswaran et al [295]. This multivariate linear regression investigated the relationship between EQ-5D utility scores and several health risk behaviours while controlling for age and gender. This tariff allowed utilities to be calculated for an actively smoking and abstaining mother at the end of pregnancy without a within-pregnancy complication. Since the utility lost for smokers was associated with the amount smoked, categorised as 'light smoker' (<10 cigarettes a day), 'moderate smoker' (10 - ≤19 cigarettes a day), and 'heavy smoker' (≥20 cigarettes a day), the average utility decrement for a smoker was calculated by taking a weighted average of the utility lost attributable to the different types of smokers within the study (Light 33%, Moderate 42%, Heavy 25%). The tariff is reported in Table 5.13.

Table 5.13: Utility tariff for smokers and non-smokers

Risk factor	Utility decrement	95% Confidence Interval
Constant	0.987	0.974 – 1
Never smoker	0	
Light smoker	0.044	0.031 - 0.058
Moderate smoker	0.055	0.041 - 0.068
Heavy smoker	0.087	0.067 - 0.107
Former smoker	0.027	0.019 - 0.036
Female	0.016	0.009 - 0.023
16-24	0	
25-34	0.015	0.005 - 0.026
35-44	0.033	0.022 - 0.044
45-54	0.068	0.056 - 0.080
55-64	0.094	0.081 - 0.107
65-74	0.166	0.101 - 0.131
75+	0.138	0.122 - 0.155
Source: Maheswaran et al **[295]**		

Chapter 2 determined that, of conditions with a potentially causal association with smoking in pregnancy, only ectopic pregnancy and miscarriage were associated with a utility loss (see Table 5.14). It was assumed there was no utility loss for the mother relating to placental abruption, placenta previa, pre-eclampsia, premature birth, and a LBW infant.

Table 5.14: Utility decrements associated with pregnancies which do not end in delivery

Condition	Mean utility decrement	Standard error
Ectopic pregnancy	0.01	0.01
Loss of pregnancy/infant (applied to ectopic pregnancy, miscarriage, and stillbirth)	0.1	0.1
Note: in the absence of information, it was assumed the standard error was the same as the mean utility decrement as a worst case scenario.		

Pregnancy does not last a full year, and therefore the life year (LY) has to be weighted by the proportion of a full year that a pregnancy lasts. There is a great deal of variation in pregnancy length. Most ectopic pregnancies are diagnosed between five and 14 weeks gestation, so 10 weeks was used as a midpoint. [296] Miscarriage can occur anytime in the first 23 weeks of gestation, although most miscarriages occur during the first trimester, before 14 weeks gestation [297], so a value of 14 weeks was chosen as midpoint. For the complications, NHS Maternity Statistics for England 2012-2013 reports numbers of births with complications by gestation. [150] The average gestation length was calculated from these data for each condition and is reported in Table 5.15.

Table 5.15: Length of gestation used to weight LYs

Condition	Premature (weeks)	Full gestation (weeks)
Ectopic	10	
Miscarriage	14	
Placental abruption	33	39
Placenta previa	33	38
Pre-eclampsia	33	39
No complication	33	40

LYs were weighted by the length of gestation, and then adjusted to take into account the utility values associated with being in a particular state, thus calculating a QALY for the MWPC. For example, the QALY for a 26 year old abstaining mother who suffers from ectopic pregnancy was calculated thus:

$$\begin{aligned} QALY = (LY \times proportion\ spent\ in\ pregnancy) \\ \times (utility\ female\ former\ smoker\ aged\ 26 \\ - utility\ decrement\ ectopic\ pregnancy) \\ = \left(1 \times \left(\frac{10}{52}\right)\right) \times \left((0.987 - 0.027 - 0.016 - 0.015) - 0.01 - 0.1\right) \\ = 0.1575 \end{aligned}$$

5.6 Estimating infant health related quality of life parameters for inclusion in the model

Utility assignments to the infant when it is inside the womb are not made. Therefore, to model the potential impact of smoking and cessation on infants during pregnancy, the model estimates the number of adverse pregnancy outcomes related to the infant. The model records the number of infants lost (miscarried, ectopic, or stillborn), born prematurely, or born with LBW. The model also reports two overall measures. The first of these is an adverse live birth, defined as any birth which is LBW or premature, but ends with the infant alive. The other measure is any adverse pregnancy outcome, defined as any foetus lost to miscarriage or ectopic pregnancy, any infant stillborn, any born with LBW and any born prematurely. Unlike the MWPC, the IWPC uses these categories as the measures of effectiveness, generating an ICER per adverse live birth, and an ICER per adverse pregnancy outcome.

5.7 Costs of healthcare attributable to pregnancy and associated complications

Estimates for healthcare costs were taken from NHS Reference Costs 2011-12, which report Healthcare Resource Groups (HRG), with the cost analysis done from an NHS and Personal Social Services perspective, given in 2011-2012 prices. [298]. Costs for different areas of healthcare were derived by using a weighted median cost as recommended by the NHS Reference Cost team [299], whereby the costs for the different HRG codes are weighted to

reflect activity in different settings; elective inpatient, elective inpatient excess bed days, non-elective inpatient (short stay), non-elective inpatient (long stay), non-elective excess bed days, day cases, regular day/night admissions, outpatients, and community midwife services. These were in turn weighted by the activity in the different settings to give a weighted median cost per hospital care. The details of the HRG codes used in the costings are given in Table 5.16. For the cost of death, the cost of cardiac event was attributed as a proxy for the cost of emergency care since there is no HRG code for obstetric death. [4] Details of the costs are given in Table 5.17.

Table 5.16: HRG codes used to identify relevant NHS Reference Costs

Condition/ Treatment	HRG codes	Description
Ectopic pregnancy	MB04A	Ovary, Fallopian Tube or Pelvic Disorders, with complication
	MB04B	Ovary, Fallopian Tube or Pelvic Disorders, without complication
Miscarriage	MB08Z	Threatened or Spontaneous Miscarriage
Ultrasound scan	NZ21Z	Ante-natal Standard Ultrasound Scan
	NZ22Z	Ante-natal Specialised Ultrasound Scan
Obstetric visits	501*	Consultant led: First attendance non-admitted face to face
	501*	Consultant led: First attendance non-admitted non face to face
	501*	Consultant led: First attendance multi-professional non-admitted face to face
	501*	Consultant led: First attendance multi-professional non-admitted non face to face
	501*	Non-consultant led: First attendance non-admitted face to face
	501*	Non-consultant led: First attendance non-admitted non face to face
	501*	Non-consultant led: First attendance multi-professional non-admitted face to face
	501*	Consultant led: Follow up non-admitted face to face
	501*	Consultant led: Follow up non-admitted non face to face
	501*	Consultant led: Follow up multi-professional non-admitted face to face
	501*	Consultant led: Follow up multi-professional non-admitted non face to face
	501*	Non-consultant led: Follow up non-admitted face to face
	501*	Non-consultant led: Follow up non-admitted non face to face
	501*	Non-consultant led: Follow up multi-professional non-admitted face to face

Birth	NZ11A	Normal Delivery with complication
	NZ11B	Normal Delivery without complication
	NZ11C	Normal Delivery with Epidural, with complication
	NZ11D	Normal Delivery with Epidural, without complication
	NZ11E	Normal Delivery with Induction, with complication
	NZ11F	Normal Delivery with Induction, without complication
	NZ11G	Normal Delivery with Post-partum Surgical Intervention
	NZ12A	Assisted Delivery with complication
	NZ12B	Assisted Delivery without complication
	NZ12C	Assisted Delivery with Epidural, with complication
	NZ12D	Assisted Delivery with Epidural, without complication
	NZ12E	Assisted Delivery with Induction, with complication
	NZ12F	Assisted Delivery with Induction, without complication
	NZ12G	Assisted Delivery with Post-partum Surgical Intervention
	NZ13A	Planned Lower Uterine Caesarean Section with complication
	NZ13B	Planned Lower Uterine Caesarean Section without complication
	NZ14A	Emergency or Upper Uterine Caesarean Section, with complication
	NZ14B	Emergency or Upper Uterine Caesarean Section, without complication
	NZ15Z	Caesarean Section with Eclampsia, Pre-eclampsia or Placenta Previa
	NZ25Z	Labour without Specified Delivery
Routine observation	NZ16Z	Ante-natal routine observation
Death	EB05Z	Cardiac Arrest

*service code for obstetrics visit

Table 5.17: Weighted means, lower quartile, and upper quartile costs for model outcomes

	Description	Weighted mean cost	Lower quartile	Upper quartile
Foetal loss	Treatment for ectopic pregnancy	£1,749.23	£1,190.46	£2,075.46
	Treatment for miscarriage	£554.70	£362.58	£671.52
Antenatal care	Community midwife visit	£53.00	£37.00	£61.00
	Standard ultrasound scan	£109.78	£60.04	£128.57
	Specialised ultrasound scan	£121.02	£74.61	£159.83
	Obstetrician first visit	£152.21	£112.95	£189.05
	Obstetrician subsequent visit	£101.13	£69.23	£118.63
Antenatal drugs	Hypertension in pregnancy drug treatment cost	£10.61 per pack of 56 tablets*		
Delivery	Birth (with or without pre-eclampsia)	£2,079.81	£1,611.56	£2,451.21
	Emergency caesarean section birth (abruption)	£3,466.59	£2,806.53	£3,970.53
	Caesarean birth (previa)	£3,413.47	£2,762.22	£3,927.02
	Routine observation (per day)	£571.15	£364.74	£760.93
Death		£1,379.02	£773.73	£1,573.62

*Data from BNF No 64, Sept 2012 **[300]**

5.7.1 Estimating maternal healthcare costs

As individuals' antenatal care is very variable, expert opinion was sought from a practising NHS midwife to determine how to attribute 'usual care' (UC) costs. Costs were attributed using the following assumptions:

- *Pregnancies not ending in delivery* (ectopic pregnancy and miscarriage): no antenatal care costs, hospital care costs from relevant HRG codes, and one ultrasound scan to diagnose the foetal loss
- *"Normal" pregnancy* ending in delivery: receive up to eight community midwife visits plus two ultrasound scans for antenatal care, and the cost of a birth. The number of antenatal visits was weighted to take into account that some mothers

give birth before 37 weeks (premature birth) and therefore receive up to six midwife visits rather than eight.

- *Placental abruption*: receive an emergency caesarean birth, at least one visit from an obstetrician, and remain in hospital for three days' routine observation. Number of antenatal visits weighted by the number of abruptions that occurred before 37 weeks: premature pregnancies received six midwife visits and full-term pregnancies received eight midwife visits.
- *Placenta Previa*: receive standard care plus an extra ultra-sound scan, up to the three obstetrician visits, and birth by caesarean section with three days' routine observation. Number of antenatal visits weighted by the number of women who give birth prematurely with previa.
- *Pre-eclampsia*: receive standard antenatal care, plus three obstetrician visits, three further ultrasound scans, three days' routine observation, and medication to lower the mother's blood pressure. According to NICE's care pathways the first line treatment is to first offer the drug labetalol orally. [301] The normal dose is a 200mg tablet taken twice a day, and the tablets are prescribed in packs of 56. Assuming a woman develops pre-eclampsia at week 20 of pregnancy, if she is premature then she will have received five packs, while if she is full gestation, she will have received six.
- *Cost of a delivery*: The cost of a delivery episode is difficult since a woman can suffer a pregnancy complication but not have a complicated birth, and vice-a-versa. Both abruption and previa require a birth by caesarean section, and costs linked with the relevant HRG codes for caesarean births were applied. However, for a normal pregnancy and delivery with pre-eclampsia, any mode of delivery was applicable, so all costs related to HRG codes associated with birth were used.
- *Cost of death*: If the mother died during pregnancy, either with or without a complication, costs of care up to that death would be incurred in addition to the cost of death itself.

5.7.2 Costs in the infant model

The majority of the costs associated with pregnancy in ESIP are maternal; however, there are also some attributable infant healthcare costs. Godfrey et al reported infants' healthcare costs gestation and birth weight. [4] To calculate the appropriate costs, those

associated with premature and LBW infants were weighted using a similar process to calculating the weighted mean in the NHS reference costs. Godfrey et al also reported a cost for a stillbirth. The costs are reproduced in Table 5.18.

Table 5.18: Costs relating to infant healthcare used in infant model

Condition	Estimated cost (£)†	Standard deviation (£)
Stillbirth	639	
Premature birth	2,648.55*	
Full gestation	824	940
LBW	2,413.79*	
NBW	835	978

Source: Godfrey et al. [4] Prices reported are for year 2006-2007

*Weighted costs across several birth weight/gestation length categories

† The study reported prices for the financial year 2006-2007, and were inflated to 2011-2012 prices using the Hospital and Community Health Services (HCHS) Pay & Price Index. **[89]** The inflation index was 1.1309.

5.8 Discussion

This chapter describes the rationale behind and development of the first stages of the ESIP model; the Maternal Within-Pregnancy Component (MWPC) and the Infant Within-Pregnancy Component (IWPC). These components model the impact of smoking and cessation on the mother and her foetus by incorporating several key conditions. ESIP is the second economic model to incorporate many of the relevant conditions, but the first to explicitly link maternal and foetal/infant experience of morbidity, such that impacts of maternal pregnancy complications on infant outcomes are modelled within it.

5.8.1 Strengths of the within-pregnancy components

MWPC and IWPC have several improvements over the previous literature. Firstly, there is a direct link between the MWPC and IWPC, allowing for complications occurring in the MWPC to impact on the outcomes for the infant in the IWPC. As far as the author is aware, this is novel in the literature. This link is important, since it reflects what actually occurs in

pregnancy. For example, maternal experience of abruption or pre-eclampsia can directly influence her chance of having a premature birth. This in turn impacts on the infant, since a prematurely-born infant is more likely to be born with LBW. It can also impact on the healthcare costs required to treat an infant, since infants who are born prematurely and/or with LBW are often associated with higher costs due to increased stays in neonatal intensive care units. [302] Although Shipp et al included placental abruption, placenta previa, and pre-eclampsia, their model does not make the link between the mother and her infant, and therefore the birth outcomes modelled for the infant could be wrong. This would suggest that the previous literature may underestimate the impact of smoking during pregnancy, potentially underestimating the cost-effectiveness of cessation during pregnancy.

ESIP, via MWPC and IWPC components, is only the second economic model to attempt to capture the impacts of smoking on ectopic pregnancy and miscarriage, which have been generally omitted from previous economic models. The omission of the conditions could imply that the previous literature is not only not capturing healthcare costs and HRQoL losses associated with these conditions, but could also be overestimating the number of conceptions which result in a live birth. This is important because the MWPC and IWPC potentially estimate the costs and HRQoL losses, as well as the number of live births, more accurately than the previous literature. Therefore, the cost-effectiveness estimates from ESIP could also be considered more precise.

MWPC and IWPC may deal with the impacts of placental abruption, placenta previa, and pre-eclampsia more appropriately than previous models. While Shipp et al had included these, both previa and abruption were grouped together in one arm, therefore not accurately predicting either the numbers of women who suffer these conditions accurately, or the different impacts of these conditions on the gestation period if premature birth had been incorporated. Conversely, the MWPC incorporates both conditions separately, allowing for the differences in both the risks of developing either of the conditions, and the birth being premature (0.4029 for abruption versus 0.2631 for previa). This is preferable when trying to accurately estimate the number of pregnancies that will suffer from these conditions and the associated impacts on the health of the mother and birth outcomes for her infant, since there would appear to be different healthcare costs and birth outcome

risks between the two conditions. Overall, this suggests that MWPC and the IWPC give more accurate costs and benefits than the previous economic models.

5.8.2 Limitations associated with the within-pregnancy components

One potential limitation is that the model assumes that women who quit are allocated the same risks of those pregnancy complications and infant birth outcomes as those who were never smokers. This assumption was made to allow some measure of effectiveness of interventions in reducing the risks of pregnancy complications and adverse birth outcomes, since smoking in pregnancy has been demonstrated to increase the risk of these outcomes. However, it could be argued that because the woman is a smoker, and is likely to have smoked for at least some part of pregnancy, usually until they find out they are pregnant, then the risks of these complications/adverse birth outcomes are likely to be higher compared to a never smoker. However, there is evidence to suggest that infants born to a mother who quits early in pregnancy have the same birth weight as those born to never smokers, and that, furthermore, women who accessed smoking cessation interventions also had infants with higher birth weights compared to smokers. [303] Although there is no evidence for the other complications, we could assume that the assumption is justified. However, it would certainly be possible to adjust the probabilities if in the future work was done which resolved this issue. For example, if an accurate measure of the probability of a delivery complication or adverse infant birth outcome amongst smoking women who quit during pregnancy was estimated, this could be incorporated into the model and the risks for the quitters could be adjusted.

Another limitation related to the smoker/non-smoker assumption is that the model assumes only two types of pregnant women with regard to smoking behaviour, those who had quit by the end of pregnancy, and those who were smoking at the end of pregnancy. This means that the described model fails to take into account any impacts of the timing and duration of any smoking cessation during pregnancy and its associated impact on pregnancy outcomes. This could be problematic as a woman who quits during the 30th week of her pregnancy may have different risks of developing smoking related complications compared to one who quits during her 10th week; however, the model currently groups both women together. This impact definitely exists for LBW, where women who quit before the third trimester (week 29) have substantially lower risks of LBW

compared to those who smoked throughout pregnancy. [304] This could lead to two impacts regarding the cost-effectiveness estimates generated by the within-pregnancy components. Firstly, the MWPC and IWPC could be slightly overestimating the number of women who benefit from smoking cessation during pregnancy, as several women could be counted as having quit who actually only quit just before the end of pregnancy. This would suggest that the model is overestimating the potential cost-effectiveness of cessation within-pregnancy. On the contrary, the model could be underestimating the number of women who benefit, since some women who have been counted as smokers may have actually been quit most of the way through pregnancy, but the model would not assign them any benefit. This would suggest the model is underestimating the potential cost-effectiveness of cessation within-pregnancy. Unfortunately, the author cannot speculate as to how much this is a problem for the results of the MWPC and the IWPC. Further empirical research is needed to identify the impact of different cessation timings on the risks of developing the conditions. This limitation is likely to remain a problem for all subsequent economic models of cessation during pregnancy until further research is conducted. However, a potential method to correct this issue would be to introduce changes in smoking behaviour (such as quitting/relapsing) at different points in the model, perhaps by trimester. This could allow the introduction of work demonstrating the effects of timing of cessation. [304] This could be one avenue for further research.

There are also some potential issues related to the costs used in the model. A brief literature search failed to identify a robust and reliable cost for a normal pregnancy. Although the model uses the weighted mean cost as recommended by the NHS Reference Cost team, and expert opinion was obtained from an experienced midwife, who gave details of the likely associated outcomes and costs, there is a high degree of variability in the antenatal and associated delivery costs, which may not have been captured. For example, data around the length of hospital stay before delivery, number of hospital visits, and number of extra scans is unavailable. However, due to the limited data available, it would prove very difficult to counteract this limitation without capturing data around resource use during pregnancy in more detail. This could mean that the model is underestimating the costs associated with not only a normal pregnancy, but also the cost of the adverse events associated with pregnancy, giving conservative estimates of the true cost to the NHS. However, these costs are a relatively small part of the model, which can be changed easily should new information become apparent.

Another possible limitation with the components is that, again due to an absence of available data, there are no utility losses associated with placental abruption, placenta previa, and pre-eclampsia; it is possible that these may have an effect on maternal quality of life. This was clearly demonstrated in section 2.4.7, where we identified no utility decrements or weights with these conditions. Indeed, one included study recommended that there was no utility loss associated with pre-eclampsia after the authors consulted expert and clinical opinion. [157] Therefore, it would seem justifiable not to include a utility loss associated with these complications. However, a mother who suffers from previa or abruption is likely to notice a very severe impact on her HRQoL; although this might only be a short term impact, it would still be relevant in the time frame of this model. Therefore the MWPC could be overestimating the HRQoL associated with women who have a delivery with a complication. This could have implications for the cost-effectiveness estimates for cessation interventions, since the model is underestimating the health related impact of these conditions. However, to solve this issue would require further research in identifying a relevant utility loss to associate with these conditions. One possible solution could be to introduce an arbitrary utility loss, and, in a sensitivity analysis, investigate what impact this has on the model outputs.

The within-pregnancy components also do not incorporate two conditions which have been identified as having a causal association with smoking during pregnancy; PROM / PPROM, and congenital anomalies. However, in most cases, PPROM and PROM result in a normal birth; therefore it could be considered that there is no significant difference in costs between those mothers who suffer from the complication compared with those who do not. [305] Furthermore, Chapter 2 did not identify that PROM / PPROM had any impact on HRQoL, and therefore its inclusion is very unlikely to change any valuation of the benefits of cessation.

For congenital anomalies, there was far more information identified suggesting that there was a greater impact on HRQoL. However, these appear to have a great deal of variation, dependent on the type of abnormality the infant has developed. This would have been an added complication to the within-pregnancy components, as to generate reasonably accurate measures of HRQoL and healthcare costs associated with the anomalies, the within-pregnancy components would probably have to differentiate between diseases with

a lasting impact and those that do not. Since the conditions also have a relatively low incidence, it is very likely that the overall impact on the results from the IWPC and any subsequent childhood model would also have been negligible, despite the significant impacts on HRQoL and healthcare costs. Although the omission of congenital anomalies and PPROM / PROM is a limitation of the components, it is unlikely that the omission of these conditions is likely to have a major impact on the results of the within-pregnancy components.

Another consideration is the utility values as reported by Maheswaran et al. [295] These values were estimated using a multivariate linear regression based on 14,117 participants aged 16 years old or greater, using EQ-5D data as collected from the 2008 Health Survey for England. The authors highlighted that there were limitations with this study, namely that: the data was self-reported and therefore susceptible to reporting bias; the survey was cross-sectional and hence it is not possible to establish temporality of the observed findings; and there could be adaptation to health states occurring, suggesting that the estimated utility decrements are not capturing the full decrement associated with the health state. These values differ slightly from those estimated by Kind et al, which have been frequently used as the population norms for utility values [306], for example a non-smoking 25 year old female has a utility weight of 0.8937 from Kind et al whereas Maheswaran et al estimate 0.956. This would suggest that the use of Maheswaran et al estimates may be overestimating the utility weights associated with the mother, and hence the model could be introducing a bias in favour of the intervention when considering its cost-effectiveness. However, the estimates generated by Kind et al were based on the results of 3,395 men and women across the UK. Maheswaran et al has approximately four times the number of participants, which suggests that it produces better estimates of the utility values. However, whereas Kind et al estimated values for the UK population, Maheswaran estimated values for England alone, and hence the utility weights can only be considered generalizable to population in England and not the UK. This will limit the generalisability of the MWPC to producing estimates of cost-effectiveness only for the population of England and not the UK, which may reduce the relevance of the cost-effectiveness estimates to the decision makers. However, more recently, Sullivan et al have estimated a series of utility decrements for the UK population based on the EQ-5D score associated with 79,197 individuals. [307] Unfortunately, while this reports utility decrements for various conditions as well as age, gender, race, and inequality, it does not

report a utility decrement for both current and former smokers, and therefore was not used in this thesis because it did not provide the relevant information.

Another consideration is that we have not reported a utility for a woman who is pregnant. It is likely that a woman who is pregnant will have a different utility value to a woman who is not pregnant; however there is some debate as to whether the generic quality of life measures (e.g. ED-5D, SF-6D) will be responsive to changes in quality of life amongst specialised populations, including pregnant women. [308] Some studies have highlighted that there appears to be no evidence on an impact on quality of life between pregnant and non-pregnant women[309], while other studies have suggested that there is a significant difference between pregnant and non-pregnant women. [310] However, the author is unaware of any utility values than have been calculated during pregnancy, which was further highlighted by Mogos et al. [308]

5.8.3 The MWPC and IWPC in context of other literature

There have been four previous report-comparable economic models. [65, 68, 190, 205] Shipp et al constructed two decision tree models to evaluate cessation in terms of pregnancy outcomes for the mother and birth outcomes for the infant. [65] For the maternal decision model, the included outcomes were placental abruption, placenta previa, pre-eclampsia, and antepartum haemorrhage, while the infant model included premature birth and full-term LBW. For the maternal model, it was assumed that there were two groups of women; those who weren't smoking at the first antenatal visit, and those who were smoking and then exposed to a cessation intervention. It has already been discussed that one improvement that the ESIP model has over Shipp et al is that the MWPC and IWPC are linked such that the pregnancy outcomes for mother have direct impacts on the birth outcomes for the infant. A second improvement over Shipp et al is that in the development of ESIP, the author has systematically identified the conditions to be included in the model. Shipp et al included antepartum haemorrhage, yet the author found no evidence that a link between smoking during pregnancy and an increased risk of haemorrhage exists. The inclusion of this condition could be potentially overestimating the negative effects of smoking, inferring that the cost-effectiveness estimates by Shipp et al are inaccurate. One final issue with Shipp is that it is unclear whether the infant model assumes that all the prematurely born infants are treated as LBW or not. As demonstrated

in Section 5.4.7, not all premature births are LBW, and therefore Shipp et al could be overestimating the number of LBW infants, increasing the imprecision of the cost-effectiveness estimates.

Both Marks et al and Hueston et al constructed models that evaluated cessation in terms of birth outcomes for the infant. [68, 205] These models were relatively simple in structure, with Marks et al estimating the impact on the number of LBW and stillbirths, and Hueston et al estimating the number of LBW. Both these models only calculate the number of events avoided, and the potential cost savings from cessation. The structures determine whether the infant has an adverse birth outcome contingent on the mother's smoking behaviour. The IWPC is an improvement on these models because it takes into account both the impact of premature birth on birth weight and the joint impact of prematurity and birth weight on stillbirth. Furthermore, because of the link with the MWPC, the IWPC is likely to produce more precise estimates of birth outcomes because it takes into account whether the mother has suffered a pregnancy complication. Therefore, the IWPC would appear to have a more encompassing structure than these two studies.

Although Mallender et al modelled cessation interventions in secondary care maternity services, the model managed to incorporate within-pregnancy outcomes. [190] A different approach was used where the prevalence of the conditions occurring within the cohort were calculated. This could be seen as potentially more flexible, in that it allows the incorporation of conditions such as PPROM, which ESIP excludes due to lack of data. However, one issue with approach used by Mallender et al is that the model approached birth outcomes for the infant (e.g. LBW) as mutually exclusive events from the mother's pregnancy outcomes. Secondly, Mallender et al has not used UK-specific prevalence data for the within-pregnancy maternal complications, even though such data exists and has been used in ESIP. Therefore, it could be argued that not only is ESIP more representative of what occurs during pregnancy, but also, from a UK perspective, it could be construed that the within-pregnancy components are generating more accurate estimates of within-pregnancy complications.

5.8.4 Implications for future research

One of the limitations of the model was attributing the correct costs, not only to the complications, but for the infant birth outcomes as well. Although there is some literature investigating the costs attributable to smoking during pregnancy for both the mother and the infant, retrieving reasonably accurate costs for the model proved to be relatively difficult. There does seem to be a great degree of variability in the costs associated with both a normal and a complicated birth, and it would certainly be beneficial if more specific costs and resource use could be identified.

Another limitation of the ESIP model which could be improved upon with further research was the link between premature birth and the mother suffering a pregnancy complication. This was only based upon one year of HES data, and might explain some why the model seems to underestimate the number of premature births. As future editions of HES data become available, the data should be incorporated into the ESIP model to see if it becomes better at estimating the impact of smoking during pregnancy on premature birth.

5.9 Summary

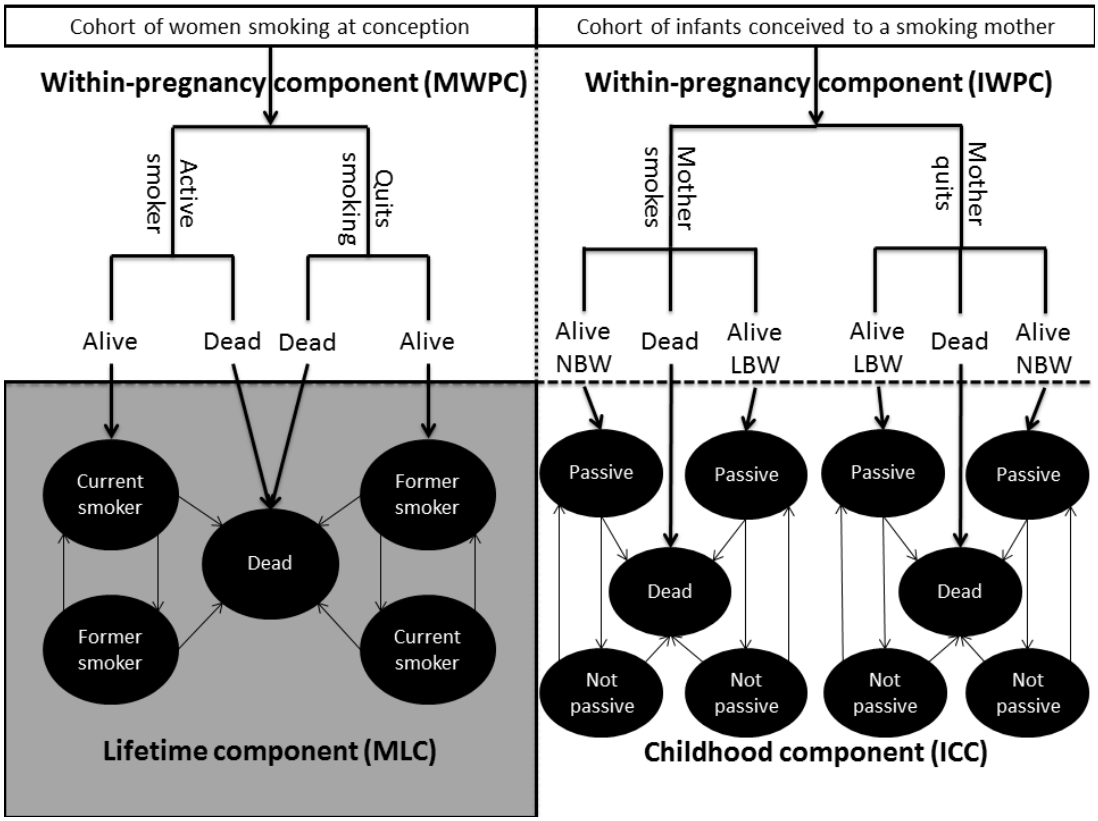
This first stage for the ESIP model is very different from previous economic models, incorporating both foetal loss and smoking-related pregnancy complications with significant impacts on costs and HRQoL. The next two chapters outline the other components of the ESIP model, which estimate the impacts maternal mother's smoking behaviour and health over her lifetime, and on infant health to 15 years old. Furthermore there is a demonstration on the validity of the within-pregnancy components (MWPC and IWPC) in Chapter 9.

Chapter 6: The Mother's Lifetime Component (MLC) of ESIP: The impacts of smoking behaviour and related morbidities

6.1 Introduction

This chapter outlines the rationale for and methods used to create an ESIP component which models maternal smoking behaviour after pregnancy and its impact on health and healthcare costs. Within the overall ESIP model, this chapter describes the structure and parameterisation of the ESIP Maternal Lifetime Component (MLC), focusing on the grey highlighted area shown in Figure 6.1.

Figure 6.1: Overall structure of the ESIP model; focus of this chapter highlighted in grey



6.2 Background

Most previous economic literature on smoking cessation interventions during pregnancy uses a 'within-pregnancy' time horizon. [137, 139, 190] Only three models extended beyond pregnancy, despite smoking being associated with increased mortality and morbidity from many diseases, including lung cancer (LC) and coronary heart disease (CHD). [9, 66] Such diseases may affect women who smoke after pregnancy and can have significant treatment costs and impacts on the health of a patient. It has been estimated that around 18% of all deaths in 2011 were attributable to smoking, and therefore could have been potentially preventable. [134] Women's smoking behaviour after pregnancy is likely to be influenced by prior smoking behaviour, and this includes decisions made prior to as well as during pregnancy. If a woman remains abstinent after pregnancy, she no longer exposes herself to potential smoking-related morbidities, resulting in a benefit which accrues after childbirth and is additional to that derived from abstinence during pregnancy itself. However, if a woman relapses after pregnancy, any long-term benefit from cessation during pregnancy is likely to be reduced, or at worst entirely negated. Clearly, for an economic model to be comprehensive, it should capture the potentially major impacts of smoking behaviour after, as well as within, pregnancy.

6.3 Aims and objectives

6.3.1 Primary objective:

To describe the ESIP component, which captures maternal smoking behaviour after pregnancy and estimates the impact on maternal lifetime health and healthcare costs.

6.3.2 Secondary objectives:

1. To outline the structure of the Mother Lifetime Component (MLC) component and how the cohort flows through the Markov chains
2. To model maternal smoking behaviour for the first two years postpartum using estimates for smoking behaviour after childbirth from Chapter 4
3. To model the smoking behaviour of mothers beyond two years postpartum for the rest of their lifetime
4. To estimate the numbers of maternal smoking related morbidities that occur amongst the cohort of women
5. To determine costs and HRQoL measures for healthy women and those suffering from a morbidity

6.4 Maternal Lifetime Component: structure

This section describes the structure of the MLC's Markov chain model which is used to determine maternal smoking behaviour after pregnancy and outlines how this is linked to the Mother Within-Pregnancy Component (MWPC). For the methods associated with Markov models, please see section 1.6.7.2.

6.4.1 Basic Markov model structure

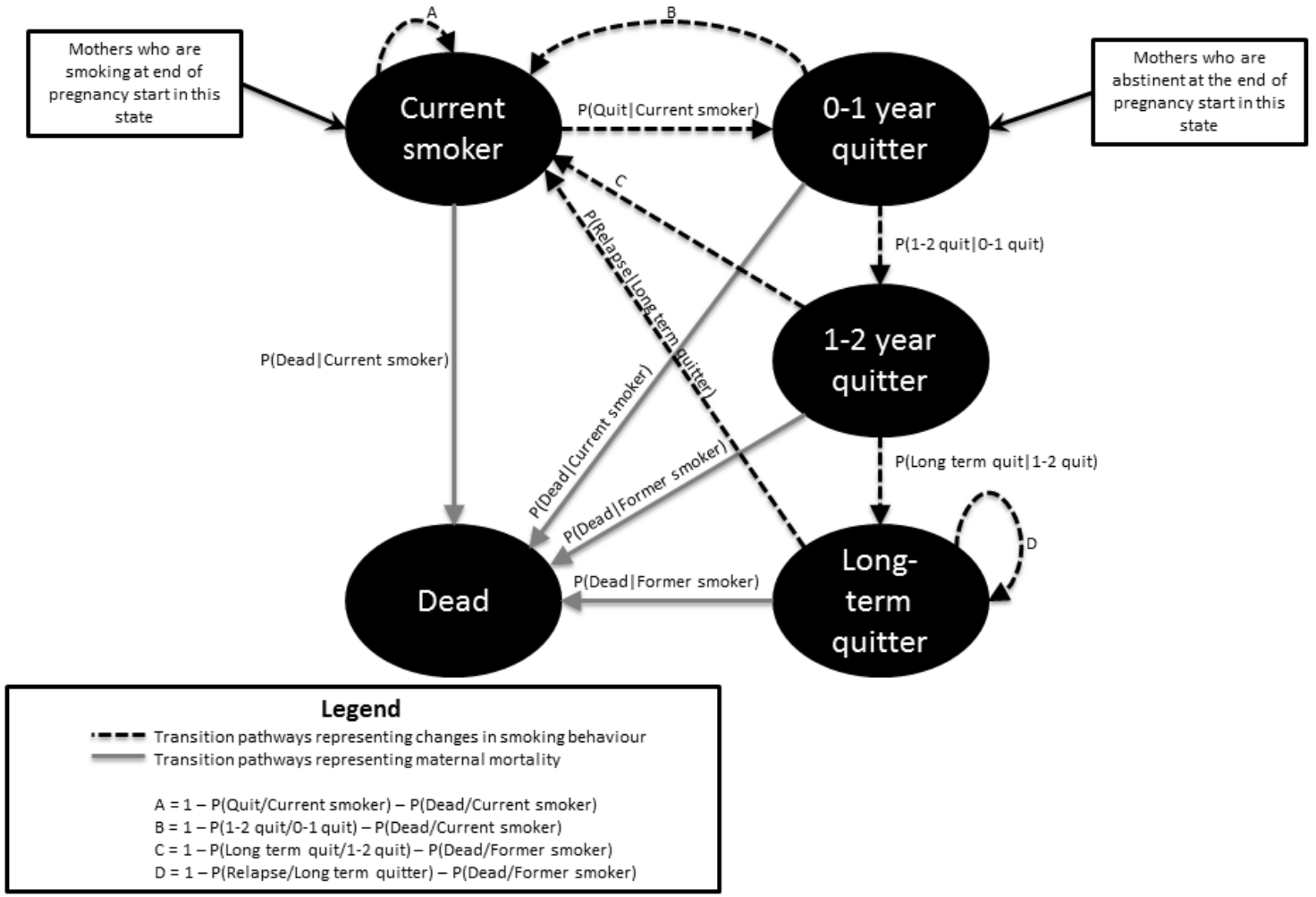
A simple Markov model predicting smoking behaviour has already been constructed, and subsequently adapted with pregnancy-related postpartum parameters. [129, 139, 190] This general smoking behaviour Markov chain had three states:

1. Current smoker
2. Former smoker: a woman who smoked and has now stopped
3. Dead

This Markov structure was deemed inadequate for the MLC because women who might only have stopped smoking for a very short time were grouped as former smokers with

others who had been abstinent for much longer. As discussed in Chapter 4, most quitters relapse within one year whether pregnant or not. [134] Therefore, it would seem logical that they would not receive any benefit because the temporary abstinence is so short, and thus by grouping the short- and long-term abstainers together, the simple Markov would overestimate the HRQoL gains in the long-term. Consequently, it is appropriate that the MLC should adopt a different structure which is more reflective of long-term smoking patterns. The new structure for the smoking behaviour model constructed for the MLC is in Figure 6.2.

Figure 6.2: Basic Markov chain structure for the Mother's Lifetime Component



The MLC contains five states which represent stages of women's smoking behaviour after pregnancy. These are:

1. Current smoker
2. 0-1 year quitter: women maintaining abstinence for 12 months or less after quit attempt
3. 1-2 years quitter: women maintaining abstinence for longer than 12 but less than 24 months after quit attempt
4. Long-term quitter: women who are abstinent from smoking for more than 24 months after quit attempt
5. Dead

The MLC adopted annual cycles, to better fit available data. Both the 0-1 year quitter and 1-2 years quitter are tunnel states; women cannot remain in these states for more than one cycle and must transit to one of the other linked states. However, they could remain in the other three states indefinitely.

In any cycle, a woman who reported active smoking could transit to three possible states: remain an active smoker; make a quit attempt (become a 0-1 year quitter); or exit the cohort by dying. The model assumes that a woman can make an unlimited number of quit attempts throughout the rest of her life. Once a woman becomes a 0-1 year quitter, she again has three possible transitions: 1-2 years quitter; relapse to smoking; or die. For a woman who becomes a 1-2 year quitter, the three possible transitions are to become a long-term quitter, relapse to smoking, or die. Because 0-1 year quitter and 1-2 years quitter are tunnel states, a woman cannot remain in them for more than one cycle. For long-term quitters, the woman again has three possible transitions: remain abstinent (i.e. stay in the long-term quitter state), relapse to active smoking, or die. This generates the transition matrix given in Table 6.1, of which the parameterisation is described in Section 6.5.

Table 6.1: Transition matrix for the MLC

Transition from:	Transition to:				
	Current smoker	0-1 year quitter	1-2 year quitter	Long-term quitter	Dead
Current smoker	$1 - P(Q_{CS}) - P(D_{CS})$	$P(Q_{CS})$	0	0	$P(D_{CS})$
0-1 year quitter	$1 - P(Q_{1Y}) - P(D_{CS})$	0	$P(Q_{1Y})$	0	$P(D_{CS})$
1-2 year quitter	$1 - P(LTQ) - P(D_{FS})$	0	0	$P(LTQ)$	$P(D_{FS})$
Long-term quitter	$P(R)$	0	0	$1 - P(R) - P(D_{FS})$	$P(D_{FS})$
Dead	0	0	0	0	1

Where: $\boldsymbol{P(Q_{CS})}$ is probability (quit|current smoker), $\boldsymbol{P(Q_{1Y})}$ is probability (quit longer than one year|quit attempt made last year), $\boldsymbol{P(LTQ)}$ is probability (quit longer than two years|quit longer than one year), $\boldsymbol{P(R)}$ is probability (relapse to smoking|quit longer than two years), $\boldsymbol{P(D_{CS})}$ is probability (dead|current smoker), $\boldsymbol{P(D_{FS})}$ is probability (dead|former smoker)

For the first two cycles after pregnancy, the MLC uses pregnancy-specific parameters for quitting and relapse behaviour. This represents the slight differences in smoking behaviour in the immediate postpartum period compared to smoking behaviour at other times outside of pregnancy. After two years, the MLC uses general smoking behaviour parameters. Both the two year postpartum-specific and the general smoking behaviour parameters are outlined in the following sections.

6.4.2 Starting states for the cohort of mothers

Mothers who have quit smoking by the end of pregnancy start the MLC in the 0-1 year quitter state, demonstrating that they have made a quit attempt for less than 12 months. Mothers who remain smoking at the end of pregnancy start the MLC in the 'current smokers' state', signifying that they are still actively smoking. This information can be found on Figure 6.2.

6.5 Parameters for the MLC representing smoking behaviour

6.5.1 Mothers who quit during pregnancy

The model utilises specific relapse data for the first two years postpartum, which are represented by the first two cycles of the MLC. Chapter 4 estimated the proportion of women who reported abstinence at one and two years after childbirth for all participants in RCTs. In the absence of more robust data, the pooled abstinence for all participants was used as a proxy for postpartum abstinence amongst the population of pregnant smokers who had received an intervention. The results from this meta-analysis are reproduced in Table 6.2.

Table 6.2: Proportion (95% CI) of women abstinent at one and two years after pregnancy

Years after pregnancy	Proportion abstinent	95% confidence interval	
End of pregnancy	0.126	0.107	0.146
1	0.074	0.027	0.122
2	0.047	-0.023	0.118

To calculate the appropriate relapse rates after pregnancy, the MLC assumes that the women who report abstinence at later time points are the same women who report abstinence at the end of pregnancy. The transition probabilities for remaining abstinent after 1 year (transiting from being a 0-1 year quitter to 1-2 year quitter) were estimated by dividing the proportion abstinent at one year after pregnancy by the proportion abstinent at the end of pregnancy. The probability of transitioning to the long-term quitter state once the mother was a 1-2 years quitter was calculated by dividing the proportion abstinent at two years postpartum by the proportion abstinent at one year postpartum. The calculated values are reported in Table 6.3.

Table 6.3: Transition probabilities for first two cycles after quitting during pregnancy

Transition probability	Calculated probability of remaining abstinent
P(1-2 quit| 0-1 quit)	0.5873
P(Long-term quit| 1-2 quit)	0.6351

6.5.2 Mothers who smoke throughout pregnancy

For mothers who smoke throughout pregnancy, there is only one parameter which is different from the general smoking behaviour parameters, and this is the probability of making a quit attempt in the first year postpartum. The latest IFS identifies that by 10 months after birth, 13% of mothers who smoked throughout pregnancy had stopped smoking. [135] Although this is not 12 months after pregnancy, it was assumed to be a close approximation. Therefore, in the first cycle only after pregnancy, the model assumes the transition probability for women who smoked throughout pregnancy to become 0-1 year quitters (make a quit attempt) is 0.13.

6.5.3 General smoking behaviour parameters for the Markov chain

The model takes a lifetime perspective, and this is imposed by allowing the cohort to reach the age of 100 years. Due to this, a general set of probabilities are required to determine the mother's smoking behaviour in the years after pregnancy. The parameters outlined below are applied in all cycles except the two immediately after pregnancy. The general values apply to both women who quit smoking during pregnancy and those who smoked throughout pregnancy.

6.5.4 General quitting behaviour amongst current smokers and short-term quitters

"Smoking in England Statistics" (Table 6.4) reported, for England in 2008/09, the percentage of female smokers who make a quit attempt in any given year and the percentage of quitters who were still abstinent at one and two years later. [134] These were the most recent available data, despite being older than other statistics used in the model. However, Table 3.6 from the Statistics on Smoking: England report gave values going back ten years to 1999 [134], with the 2008/09 estimates appearing to be a good match to the previous ten years, and since there was no evidence of a change in quitting behaviour over these ten years, with the percentage of women making quit attempts fluctuating to no distinct pattern, it seemed appropriate to use these values.

Table 6.4: Percentage of smokers who made any quit attempt last year and the length of time abstinent amongst those who those who those who have tried to give up.

	Percentage (%)	Source
Current smoker making any quit attempt in a given year	27	Table 3.6 Statistics on Smoking: England [134]
Quitters who are abstinent for more than one year but less than two	6	Table 3.7 Statistics on Smoking: England [134]
Quitters who are abstinent for more than two years	8	Table 3.7 Statistics on Smoking: England [134]

The transition probability for a current smoker to become a quitter (0-1 year quitter) is 0.27, as 27% of current smokers made any quit attempt in the last year, regardless of whether the attempt successful or not. The transition probability for 0-1 year quitter to remain abstinent (become a 1-2 years quitter) is 0.14, as this is the sum of the percentage of quitters who are still abstinent at 1 year (6% + 8% = 14%). This means that 86% of those who made a quit attempt in the previous cycle are not successful at abstaining for more than one year. The transition probability for a 1-2 years quitter to remain abstinent (become a long-term quitter) is 0.57, which is calculated by dividing 8% by 14% (the percentages of women abstinent for more than two years and more than one year but less

than two years respectively). This means that 43% of those that had successful remained abstinent for one year relapse to smoking before two years.

6.5.5 Long-term relapse rates

Yudkin et al reported relapse to smoking for up to eight years after a randomised trial of NRT. [311] This study reported abstinence at one year and eight years. The relevant data is displayed in Table 6.5.

Table 6.5: Number of smokers abstinent at one year and eight years after a smoking cessation intervention

Time period	Numbers (all participants in trial)
Abstinent at one year	153
Abstinent at eight years	83
Relapse between one and eight years	70
Source: Yudkin et al **[311]**	

The MLC requires a transition probability to reflect the propensity of women entering the long-term quitter state, after having been abstinent for two years. By multiplying the number of women abstinent in Yudkin's trial (153) by 0.57 (the transition probability identified in the section above), the number of women abstinent at the end of two years in this trial was estimated as 87. Using this figure along with data in Table 6.3, this suggests that approximately four participants relapsed between two and eight years in this trial; so dividing four by 87, the probability of relapse between years two and eight was estimated at 0.0507 and this was converted into an annual probability of 0.0086 using the method outlined by Fleurence et al. [312] This value was applied to all women in the long-term quitter state for all cycles of the model. Table 6.6 reports all the transition probabilities for women's smoking behaviour in general, which are applied from two years after pregnancy onwards.

Table 6.6: Transition probabilities for general smoking behaviour outside of two years postpartum

Smoking behaviour	Transition probability
Quit attempt given current smoker	0.27
Remain abstinent for one year	0.14
Remain abstinent for a second year after one year of not smoking	0.57
Relapse to smoking in any given year following at least two years of abstinence	0.0086

6.6 Mortality in the Markov contingent of smoking status

To estimate the number of women who die in each Markov cycle, the transition probability for death was taken from ONS Cohort Life tables, Table B1. [313]; these estimated mortality rates by age, to age 100, for women born from 1981 to 2012, and projections for women born up to 2062.[42] Doll et al demonstrated that mortality rates differ for smokers, former smokers, and never smokers, with the highest rates of mortality amongst smokers compared to never smokers.[9, 66] The estimates are reported in Table 6.7.

Table 6.7: Rates of mortality per 1,000 people by age, contingent on smoking status

Age	Current smokers	Former smokers	Never smokers
35-44	2.8	2	1.6
45-54	8.1	4.9	4
55-64	20.3	13.4	9.5
65-74	47	31.6	23.7
75-84	106	77.3	67.4
85+	218.7	179.7	168.6
Source: Table 6, Doll et al, **[66]**			

[42] Please note: due to constraints on thesis length, all values have not been reproduced in this document. However, the ONS data as used by ESIP can be found under the "ONS mortality stats" tab in the ESIP spreadsheet.

The above rates were converted to relative risks for current smokers versus never smokers and former smokers versus never smokers by dividing the current smoking/former smoking mortality rates by the never smoker ones (Table 6.8). Since Doll et al did not report any data for mortality before the age of 35, it was assumed that smoking status had no impact on mortality in women aged 34 years or less.

Table 6.8: Relative risk of death by age, contingent on smoking status

Age	Current smoker	Former smoker	Never smoker
0-34	1	1	1
35-44	1.7500	1.2500	1
45-54	2.0250	1.2250	1
55-64	2.1368	1.4105	1
65-74	1.9831	1.3333	1
75-84	1.5727	1.1469	1
85+	1.2972	1.0658	1

The ONS estimates give a general mortality probability for all women, which needed adjusting to account for the impact of smoking on mortality risk. This is required as the MLC is a smoking behaviour model, and therefore it is important to capture the impact of the higher death rates amongst current smokers and former smokers compared to never smokers. To adjust the general mortality probability, the same approach was used as described in Taylor and Flack et al [129, 139]. It can be assumed that this general population mortality probability is calculated using the following equation:

$$P(death_{GP}) = (P(death_{CS}) \times E) + (P(death_{FS}) \times F) + (P(death_{NS}) \times G) \quad (6.1)$$

Where E is the prevalence of current smokers, F is the prevalence of former smokers, G is the prevalence of never smokers, $P(death_{GP})$ is the probability of death in the overall population, $P(death_{CS})$ is the probability of death amongst current smokers, $P(death_{FS})$

is the probability of death amongst former smokers, and $P(death_{NS})$ is the probability of death amongst never smokers.

Using relative risks for mortality amongst current smokers and former smokers compared to never smokers, it can be assumed that:

$$P(death_{CS}) = RR_{CS} \times P(death_{NS}) \tag{6.2}$$

$$P(death_{FS}) = RR_{FS} \times P(death_{FS}) \tag{6.3}$$

Where RR_{CS} is the relative risk of death for current smokers, and RR_{FS} is the relative risk of death for former smokers.

Substituting equations (6.2) and (6.3) into (6.1) and rearranging allows the probability of mortality for never smokers:

$$P(death_{NS}) = \frac{P(death_{GP})}{G + (RR_{FS} \times F) + (RR_{CS} \times E)} \tag{6.4}$$

The resulting probability for (6.4) can then be substituted in (6.2) and (6.1) to generate the probability of mortality amongst former and current smokers.

The prevalence of smoking by age amongst women was taken from the latest smoking statistics for England.[134] This is reproduced in Table 6.9. For ages 0-15, it was assumed that the prevalence of current and former smokers was zero.

Table 6.9: Prevalence of smoking by age

Age	Current smoker (%)	Former smoker (%)	Never smoker (%)
16-19	19	4	77
20-24	28	7	65
25-34	21	18	61
35-49	23	22	55
50-59	18	24	58
60+	12	30	58
Source: Table 2.1, Statistics on smoking, England, 2013 **[134]**			

6.6.1 How smoking contingent mortalities were applied in the model

The probability of death for women in the current smoker state was the probability of death associated with current smokers, while women in the 1-2 years quitter and long-term quitter states received the probability of death associated with former smokers. Because most quit attempts tend to last less than 12 months, women in the 0-1 year quitter state received the probability of death associated with current smokers. This introduced a one year lag in gaining a reduced risk of mortality amongst women making a quit attempt.

6.7 Prevalence of smoking related diseases

Cigarette smoking has been attributed to increased risks of several conditions, including Coronary Heart Disease (CHD) [314], Chronic Obstructive Pulmonary Disorder (COPD) [66], lung cancer (LC) [66], and stroke. [302] Any smoking behaviour model should include these diseases as they pose a significant impact on HRQoL and healthcare costs. Although not included as states in the Markov cohort model, Taylor and Flack et al calculated the prevalence of five smoking related diseases amongst women each cycle. [129, 139] These conditions were CHD, COPD, LC, MI, and stroke.

The MLC adopts the same approach, including four smoking-related chronic conditions: CHD, COPD, LC, and stroke. In each cycle, the prevalence of each disease contingent on smoking status was calculated amongst the current and former smokers which were alive, and those who were identified as having a smoking related morbidity were attributed relevant healthcare costs and QALYs.

MI is an acute condition, heavily associated with CHD. Since it is acute, it is possible for people to only suffer from an MI for a short period, and recover fully within the timespan of a cycle, unlike a stroke where the impacts on HRQoL can be permanent. Also, the association with CHD meant there was the possibility of double-counting some of the healthcare costs. As a result of these considerations, MI was excluded from the model.

Data on the prevalence of each condition by age and sex (if possible) was sought. The prevalence of each smoking related morbidity amongst the UK female population is given in Appendix 12.7.

6.7.1 Determining the prevalence of the smoking related morbidities contingent of smoking status

For a UK model, evidence was sought for the relative risks of smoking associated with the four smoking related morbidities from UK sources; unfortunately no suitable UK information was identified. However, both Flack et al and subsequently Taylor used the relative risks from the US Surgeon General's report [129, 139, 143], and this was deemed acceptable. Therefore, the authors concluded that in the absence of better parameter estimates, and given that it corresponded with the previous literature, these estimates would be used for the MLC. The US General Surgeon's report estimates a series of relative risks for current and former smokers for use in their Smoking-Attributable Morbidity, Mortality, and Economic Costs (SAMMEC) model [143], and these are reported in Table 6.10. The MLC used these relative risks, combining them with the prevalence data reported in Appendix 12.7 and the incidence of smoking by age from Table 6.9 to determine the

prevalence of morbidities amongst current and former smokers, using the method as described in Section 6.6.

Table 6.10: Relative risks of smoking related morbidities for females by age and smoking status

Age	Current smokers				Former smokers			
	CHD	COPD	LC	Stroke*	CHD	COPD	LC	Stroke*
35-54	4.98	6.43	13.30	2.44	2.23	1.85	2.64	1.00
55-64	3.25	9.00	18.95	1.98	1.21	4.84	5.00	1.10
65-74	3.29	38.89	23.65	2.27	1.56	15.72	6.80	1.24
75+	2.25	20.96	23.08	1.70	1.42	7.06	6.38	1.10
*= RR are for cerebrovascular disease								
Source = Table 12.3 US Surgeon General report **[143]**								

6.7.2 Worked example: calculating the smoking status contingent prevalence of CHD

Below is a worked example illustrating how the prevalence of CHD was incorporated into the MLC. From Table 12.7 in Appendix 12.7 the prevalence estimate of CHD amongst 50 year old women is 1.3%.

To estimate the prevalence of CHD amongst current smokers aged 50, the following calculation was performed:

$$CHD_{NS50} = \frac{CHD_{50}}{(E_{50} \times RRCHD_{CS50}) + (F_{50} \times RRCHD_{FS50}) + G_{50}} \quad (6.5)$$

Where CHD_{50} is the prevalence of CHD amongst all 50 year olds, CHD_{NS50} is the prevalence of CHD amongst all 50 year old never smokers, E_{50} is the prevalence of current smoking amongst 50 year olds, $RRCHD_{CS50}$ is the relative risk of CHD amongst 50 year old current smokers, F_{50} is the prevalence of former smoking amongst 50 year olds, $RRCHD_{FS50}$ is the relative risk of CHD amongst 50 year old former smokers, and G_{50} is the prevalence of never smoking amongst 50 year olds.

$$CHD_{NS50} = \frac{0.013}{(0.18 \times 4.98) + (0.24 \times 2.23) + 0.58} = 0.0065$$

$$CHD_{CS50} = 0.0065 \times 4.98 = 0.0322$$

This implies that the prevalence of CHD amongst current smokers at age 50 is 3.22%. By applying the relevant relative risk for former smoker, the prevalence of CHD amongst former smokers is 1.44%.

6.7.3 How the smoking-contingent prevalences were applied in the MLC

In the MLC, there are four possible smoking behaviours for women. Those in the current smoking state received the prevalence of the diseases associated with current smoking, which represents the percentage of women who suffer from the disease given that they are current smokers. To calculate the number of women who have each of the four diseases in each cycle, the number of women in the current smoking state was multiplied by the prevalence of the disease for current smokers, thus generating an estimate of the number of current smokers who have one of the smoking related morbidities in each of the cycles. Women in the 1-2 years quitter and long-term quitter states received the prevalence of diseases associated with former smokers, and the process of multiplying the prevalence of the disease given a former smoker by the number of women in each of the abstinent states for each cycle was repeated. Because most quit attempts last less than 12 months, women in the 0-1 year quitter state received the same prevalence of diseases as current smokers. This was then applied using the same method as described above. This introduced a one year time lag in gaining a benefit in reduced risks of diseases by quitting smoking.

6.8 Health related quality of life measures

To allow the MLC to link with the MWPC, QALYs were used as the measure of HRQoL. Utilities reported by Mashewaran et al were used as outlined in Chapter 5 to calculate utility associated with current and former smokers in the cohort who did not experience any of the four smoking related morbidities outlined above. [295] For cohort members who developed co-morbidity, utility weights from Table 6.11 were used. Utilities associated with active smoking were awarded to women in the current smoker and 0-1 year quitter states, while women in the 1-2 years quitter and long-term quitter states received utilities associated with former smokers. The life year was then weighted by the utility to calculate QALYs, which were discounted by 3.5%, as recommended by the NICE reference case. [36]

Table 6.11: QALY weights associated with smoking related morbidities

Condition	Mean utility score	Standard deviation	Source
CHD	0.73	0.30*	MEDMAN study [315]
COPD	0.73	0.23	Starkie et al [316]
LC	0.67	0.22	Pickard et al [317]
Stroke	0.72	0.32	Haacke et al [318]
*= Inter quartile range used as proxy			

6.9 Costs associated with smoking related diseases

The model assumes that a cohort member who experiences none of the four included morbidities generates no cost to the NHS. Therefore, the only required costs were associated with those who developed these diseases. In keeping with the NHS and Personal Social Services Research Unit (PSSRU) perspective, the direct healthcare costs of diseases were identified from relevant literature on the economic burden of the disease, which identified a per patient annual cost to the NHS, and are reported in Table 6.12. Chapter 5 identified the cost of a cardiac event, used as a proxy for the cost of a death; this was also applied in the lifetime model and was estimated at £1,379.02 (interquartile range of £799.89). Costs were discounted at a rate of 3.5% per annum, as recommended by the

NICE reference case. [36] The number of cohort members with a particular disease for each age was multiplied by the cost per patient for each respective morbidity, to give an estimated cost to the NHS of treating smoking related diseases. The number of cohort members dying in each cycle was multiplied by the cost of death.

Table 6.12: Per patient annual cost associated with smoking related diseases

Condition	Cost (£)	Standard error (£)	Source	Notes
CHD	1,772.13	Not available	Liu et al [319]	1999 prices, inflation index 1.497879
COPD	813.14	Not available	European Respiratory Society [320]	2011 prices in euros reported, converted 08/09/2014, 1 EUR = 0.8026 GBP
LC	9,209.42	Not available	European Respiratory Society [320]	2011 prices in euros reported, converted 08/09/2014, 1 EUR = 0.8026 GBP
Stroke	20,939.20	147.96	Youman et al [321]	2001/2002 prices, inflation index 1.368039

6.10 **Discussion**

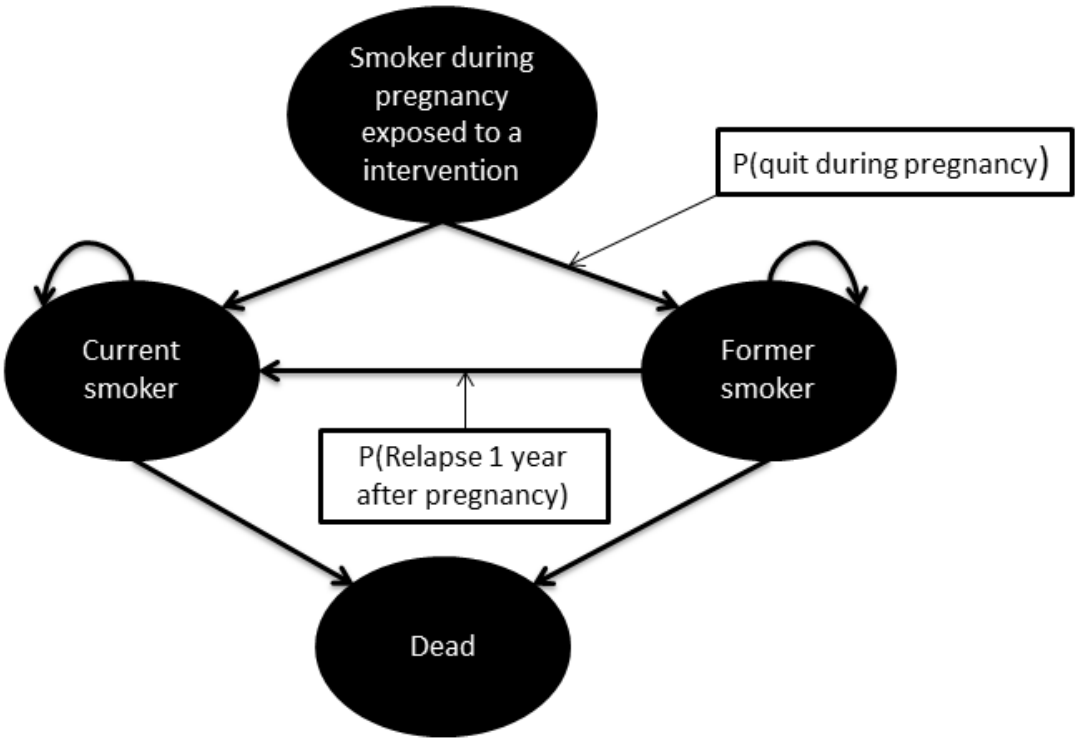
This chapter has outlined the justification and methods for the mother's lifetime component of the ESIP model. The MLC attempts to capture the impact of smoking behaviour during pregnancy on subsequent maternal smoking behaviour throughout her lifetime, future healthcare costs and quality of life lost attributable to this.

6.10.1 Comparison of MLC to previous economic evaluations

There are currently four previous models which attempt to capture the impact of smoking cessation during pregnancy on the lifetime of the mother. [137, 139, 190, 196] Ruger extended their model to a maternal lifetime perspective by estimating an average QALY across healthy individuals and individuals who suffered from either LC or CHD. The different QALYs for smokers and non-smokers were generated by assuming that a higher percentage of smokers suffered chronic conditions. The non-smoking QALY estimate also took into account that 35% of individuals who quit during pregnancy would relapse over their remaining lifetime This is neither a decision tree nor a Markov model approach, which makes comparison with the MLC challenging, despite the fact that the MLC too generates QALY gains for both quitters and smokers during pregnancy across their remaining lifetime. It could be argued that Ruger et al is not controlling for post-pregnancy smoking behaviour, which potentially means that the QALY estimates are inaccurate. Furthermore, the MLC uses pregnancy specific postpartum relapse data, which has a much higher relapse rate compared to Ruger et al, whose relapse value is from a male and female population. Therefore, it could be construed that the MLC is more precise in estimating HRQoL across the remaining lifetime.

As has been mentioned in Section 6.4.1, Taylor adapted a general smoking behaviour model to a cohort of pregnant smokers. [139] The structure has already been briefly described in that section, but the Markov chain is demonstrated in Figure 6.3. The MLC has a more complex representation of women's smoking behaviour across their lifetime and makes particular use of new data on relapse to smoking in the two years immediately after childbirth and, as such, may model the impacts of smoking on maternal health more accurately.

Figure 6.3: Structure of Markov chain model by Taylor



The model by Taylor assumed that once a woman made a quit attempt, they automatically had a better quality of life and lower risks of mortality and morbidity. This could be unrealistic, as there may be a time lag between the start of the quit attempt and when the woman actually achieves a gain in HRQoL and lower risks of mortality/morbidity. Doll et al demonstrated that the earlier in life an individual stopped smoking, the faster the risks associated with mortality/morbidity became closer to the risks in never smokers. [9, 66] The MLC introduces a one year time lag between when the woman starts a quit attempt and when she starts to receive gains in terms of reduced smoking related disease risks and HRQoL. This would suggest that the MLC is more accurate at predicting the number of women with a smoking related morbidity and/or mortality, which implies that the estimates of smoking-related healthcare costs and HRQoL are more accurate, providing more precise estimates of the cost-effectiveness of cessation interventions during pregnancy in the long-term smoking behaviour of the mother. Whether or not a one year time lag is enough is unclear, and could be a potential consideration for further research.

The slightly different structure of the MLC, with tunnel states for quitters under two years, could also be argued as being more representative of the changes in smoking behaviour. Taylor assumed that 70% of women would relapse after one year, and that there was no relapse after this. However, as the estimates from Smoking Statistics for England suggest, most women have relapsed to smoking before two years after the quit attempt, with around only 8% reporting abstinence. [134] This implies that by excluding relapse after one year, the Taylor model is underestimating the number of women who relapse to smoking by a considerable margin, thus overestimating the benefits from cessation interventions. Furthermore, the MLC allows for smoking women to make quit attempts after pregnancy. Smoking Statistics for England identified that in 2009, 27% of women made a quit attempt. [134] The Taylor structure does not allow for any subsequent quit attempts, and therefore does not capture the benefits that may occur in the longer term. The MLC allows for these quit attempts, and therefore is potentially more accurate at calculating long-term costs and QALYs for the cohort of pregnant smokers.

Furthermore, the MLC has the added advantage of using pregnancy-specific relapse and quitting data for the first two cycles of the Markov chain. Taylor used expert opinion for informing the one year postpartum relapse rate. In the hierarchy of evidence proposed by Evans et al [148], expert opinion is considered the lowest form of evidence for evaluating interventions. Conversely, the MLC uses data from a systematic review, which is considered the best available evidence for the evaluation of interventions. Therefore the MLC is more likely to be accurately modelling the smoking behaviour of mothers in the postpartum period, especially for relapse rates.

The model constructed by Mallender et al [190] adopted the same structure as Taylor, with two key differences: first of all, the quit rate after the first cycle was determined by the estimates associated with the interventions that were modelled, added to which was an arbitrary quit rate of 2% in each subsequent cycle. Secondly, Mallender et al assumed that the relapse rate was zero, arguing that the 2% added bonus represented the rate of all women who quit permanently. The MLC makes no such assumptions, since data given by Yudkin et al demonstrates that these assumptions are unrealistic. [311] Although most people who have been abstinent for longer than two years remain permanently so, a small

proportion will relapse to smoking over time; therefore a 0% relapse rate is too optimistic an assumption. Furthermore, the simplified structure adopted by both Taylor and Mallender et al fails to represent the major changes seen in smoking behaviour both around and beyond pregnancy, as has been detailed above.

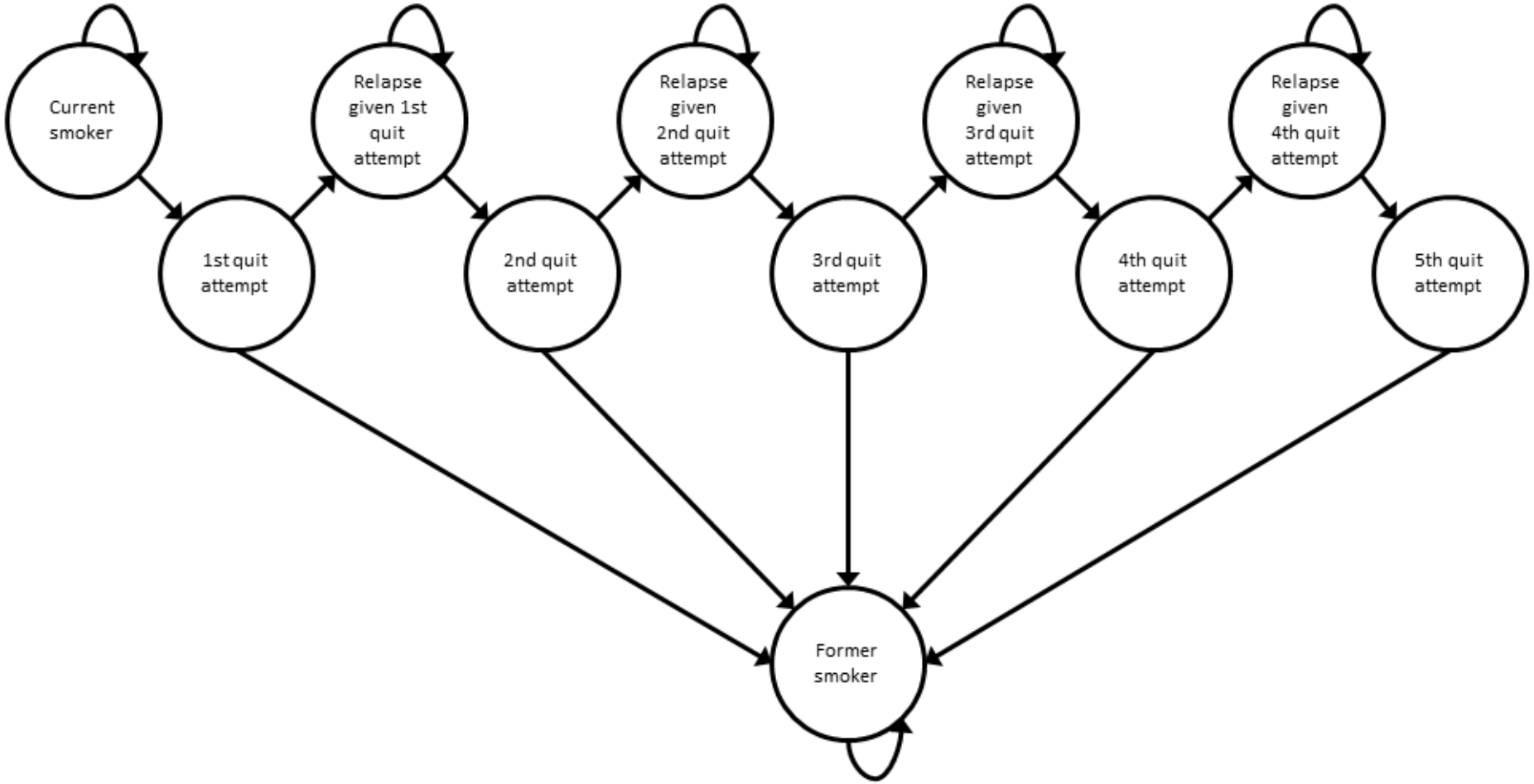
Tappin et al extended their within-trial analysis to incorporate the maternal lifetime by adapting a previously developed Markov model to calculate QALYs, healthcare costs, and smoking-attributable deaths. [196, 209] The Markov structure was virtually identical to Taylor, except that there were two death states: smoking-attributable deaths and non-smoking-attributable deaths. Tappin et al improved on Taylor by allowing relapse to extend beyond one year postpartum, but the rates were informed by studies in non-pregnant populations. [311, 322] While this model improves on previous literature by capturing relapse up to eight years after pregnancy, the MLC incorporates some measure of longer term relapse, therefore capturing the impacts on costs and benefits accrued from this. Furthermore, Tappin et al do not allow for any subsequent quit attempts, which is included in the MLC, hence the MLC could be better capturing long-term maternal smoking behaviour. One final consideration is that Tappin et al did not include the impacts on HRQoL from long-term smoking related diseases, which are integrated in the MLC. Tappin et al did, however, attempt to estimate the total healthcare costs associated with a smoking related death, and therefore these may be viewed as providing further evidence on the long-term costs associated with smoking.

6.10.2 Limitations of the MLC

There are several limitations of the MLC model. Firstly, the MLC model does not incorporate any subsequent pregnancies. Some women are likely to have more than one child, and therefore may attempt to quit smoking again during pregnancy, and face the same risks and outcomes as they initially faced in the first stage of ESIP. This was not included in MLC, due to the complexity faced in incorporating such potential events, which is beyond the scope of the current project. MLC may not, therefore, be completely representative of women's smoking behaviour after pregnancy, but the implications of this omission are not known.

MLC also allows women to make numerous quit attempts after pregnancy, due to the Markov assumption which asserts that the Markov model is memoryless. This lack of memory means that a relapsing woman can make many quit attempts, which could be unrealistic. There is evidence to suggest that the more quit attempts an individual makes, the more likely that they are to successfully quit smoking [323-326], with Caponnetto estimating that women who had made previous long-term quit attempts lasting longer than one year were 36% more likely to quit. [323] Furthermore, it has been estimated that it takes on average a woman 6.3 quit attempts across her lifetime to become a former smoker. [327] Because of the Markov assumption, women who relapse can make another quit attempt, but there is no limit to the number they make. The evidence suggests that in reality that women need only make six or seven attempts before they quit for good, and that the transition probabilities will change with each quit attempt to reflect their greater chance of success. Unfortunately, the model does not capture this behaviour, and therefore could be underestimating the number of women who have successfully quit in future cycles. This would mean that the MLC is not capturing the full benefits generated by cessation interventions, and hence the ICERs generated by the MLC could be too high, underestimating the cost-effectiveness of cessation interventions. One approach to correct this may be to introduce another series of states to represent previous history of quit attempts. Figure 6.4 gives an example of what the structure of this Markov might be.

Figure 6.4: Example Markov structure for modelling quitting behaviour based on previous quitting behaviour, assuming a woman takes up to five quit attempts before becoming a successful former smoker



As can be seen from Figure 6.4, to capture the previous history of the mother's smoking and quitting behaviour would require a large number of additional states in the Markov, adding to the complexity of the MLC. Adopting this structure for modelling smoker behaviour would probably enable the MLC to better estimate smoking behaviour across the mother's lifetime, and hence produce more accurate healthcare cost estimations and QALY estimates across the cohort of women's lifetime, enabling more precise estimates of the ICER and value for money of the interventions. However, a Markov model with this complexity would be very difficult to parameterise, and hence estimates for the transition probabilities in later states may be reliant on poor sources of data which could introduce bias and increase decision uncertainty in the evaluation. Furthermore, we are uncertain how many additional quitting/relapse states would be required. Although we have the estimate of 6.3 average quit attempts [327], this was based on US data, and UK women may require more (or fewer). Additionally, there would have to be extra analyses while the structural uncertainty associated with the number of additional quitting/relapse states were added, which would increase complexity in undertaking the evaluation. Therefore, the authors speculate that the introduction of this added complexity would not be of benefit to the evaluations of smoking cessation interventions with the current level of information; however consideration could be given to adopting this structure should sufficient evidence become available in the future.

The MLC includes fewer smoking-related chronic morbidities than other models. The Taylor model added MI [139], and the SAMMEC model, which estimated only costs, incorporated a further seven diseases in addition to those given in the MLC. [143] As discussed in Section 6.7, although there are substantial healthcare costs associated with MI, it is an acute condition, as it is possible for a heart attack sufferer to regain her previous health within one cycle of the model, and it is also heavily associated with CHD, leading to potential double-counting of healthcare costs. It was consequently excluded, as the MLC was primarily interested in chronic conditions as these tend to have the highest healthcare costs and impacts on HRQoL, and are therefore seen as the more important morbidities for inclusion. The exclusion of MI could potentially lead the MLC to underestimate the gains from quitting, however the chronic conditions included in the MLC all have extensive costs and health outcomes; thus the MLC is likely to capture most of the costs and health related outcomes associated with poor health due to smoking related behaviour. Furthermore, in

comparison with the SAMMEC model, the conditions which have the highest relative risks associated with smoking status are the four conditions included in the model, suggesting that it is capturing the most important conditions associated with smoking behaviour.

One possible limitation is the use of group abstinence data rather than longitudinal relapse data from the Chapter 4 review. As pointed out in Chapter 4, it is not known whether the women who reported abstinence in the postpartum periods were the same women who reported abstinence at the end of pregnancy. True relapse rates can only be accurately measured amongst smokers who are abstinent initially and who remain abstinent when followed up, but our data is derived in a different way. This could result in MLC biased estimates of the proportion of smokers who relapse in the postpartum period. However, as was identified in Chapter 4, there are relatively few studies in which sustained abstinence across the postpartum period is reported, and the data in the systematic review is the best available at the current moment in time, implying that the MLC is constructed with the most up-to-date data.

Another consideration is the small probability of relapse estimated from Yudkin et al which was applied to the long-term quitter state for all subsequent cycles of the model. [311] Yudkin et al have suggested that there is very little relapse beyond eight years [311], and that the MLC assumption of applying this small probability of relapse across all subsequent cycles would appear to be incorrect. However, the reasoning behind including this probability was that long-term quitters can still relapse to smoking, even after many years of being abstinent. Hawkins et al demonstrated that even 13 years after making a quit attempt, individuals were still relapsing. [328] This would suggest that the assumption of allowing long-term quitters to relapse irrespective as to how long they have been abstinent would appear to be correct. However, if this assumption is incorrect, then the MLC is likely to be overestimating the number of women who have relapsed to smoking, and hence the ICER estimates generated by the MLC are likely to be higher than the true value. One possible way of preventing this would be to introduce a series of tunnel states up to eight years post quit attempt, but this is likely to add to the complexity of the model, and would not capture those women who relapse much further after the quit attempt.

6.10.3 Future improvements for the MLC

One important consideration is the relapse to smoking rates associated with quitting during pregnancy, and there are two possible avenues for further improvement. First of all, more accurate sustained postpartum abstinence data would be useful to accurately estimate relapse, though this would require several new studies, all measuring prolonged cessation at similar postpartum time points. A second improvement could be the incorporation of intervention specific rather than general intervention data. It would seem likely that different interventions would have different relapse rates after pregnancy, and currently the MLC has not been calibrated to capture this. However, data on postpartum relapse by intervention is extremely limited, so again this would require a significant amount of further research to generate appropriate data.

Another improvement would be to better capture quit attempts in the remaining lifetime outside of the two year postpartum period. Relapse after quitting may change due to age or the number of previous quit attempts. Currently the MLC assumes that the relapse and quit rates is fixed across all ages after two years postpartum, which could be inaccurate. Incorporating data around the number of quit attempts before success (or ultimate failure) would allow the MLC to more accurately predict subsequent smoking behaviour. Further research should be conducted to determine whether relapse rates do change by age or by previous quit attempts. While changes in age would be relatively easy to incorporate into the MLC, it may be trickier to include subsequent quit attempts. This may be possible by incorporating a further series of tunnel states; however, this would add a further layer of complexity to the model.

Another potential problem is the difference between short- and long-term quitters when attributing risks of morbidities and mortality. At the moment, the MLC has a built in lag of one year before quitters gain any benefit from quitting. This could be expanded to better estimate the impacts of quitting earlier in life compared with those who quit later. Again, through the use of tunnel states, it may be possible to incorporate a lag of five or 10 years into the MLC. The risks when applied to women in these states would thus be dependent on whether a woman has been quit for five or ten years. This would allow the model to

better capture the number of women who develop a smoking related morbidity, or die as a result of smoking. However, to incorporate this into the model, further research would also have to be done into the relapse rates associated with these states, otherwise the ESIP model may end up overestimating the number of women who have been quit in the longer time periods.

6.11 Summary

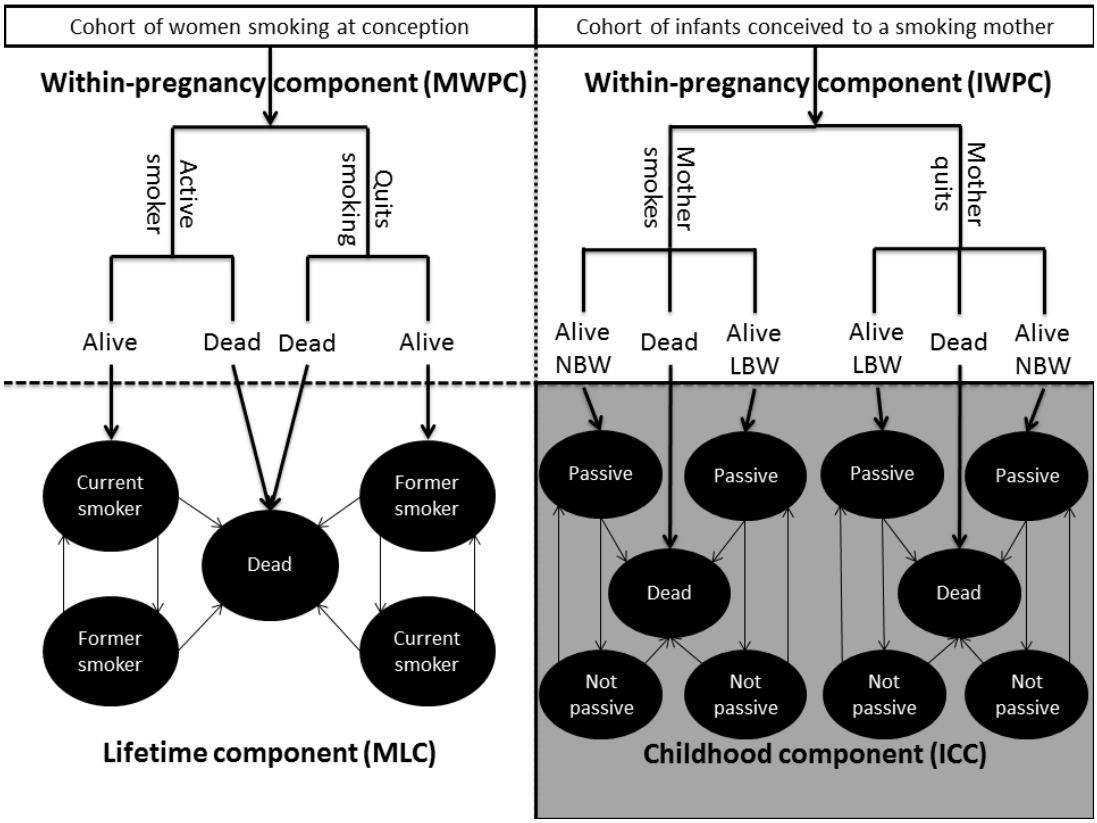
This chapter has outlined the MLC of ESIP and shows that women's lifetime smoking behaviour and associated morbidities are important considerations for inclusion in economic evaluations of cessation during pregnancy. Compared to the previous models, the MLC may be better for predicting maternal smoking behaviour, however there are still some areas of the MLC which require improvement. Chapter 7 describes the structure of the Infant Childhood Component (ICC), which predicts the impact of the mother's smoking during childhood on the health of her offspring.

Chapter 7: The ESIP model: Description of the childhood component

7.1 Introduction

Previous chapters outlined the maternal 'within pregnancy' and 'lifetime' components of the ESIP model. This chapter describes the rationale and methods used in the construction of the 'childhood' component of the ESIP model, covering the impacts of maternal smoking on infants up to the age of 15 years. This is represented in Figure 7.1 as the shaded part of the ESIP model. This component shall be henceforth referred to as the Infant Childhood Component (ICC).

Figure 7.1: The Infant Childhood Component (grey area) within context of the ESIP model



7.2 Background

Only two previous economic models have attempted to consider the impacts of smoking across infant lives. [139, 190] Chapter 2 identified that maternal smoking in pregnancy appears to have a causal relationship with childhood respiratory illness. Smoking during pregnancy can have potentially life changing/threatening impacts on the health of the child, leading to an increased cost burden to the NHS, especially if there are thousands of cases of potentially preventable chronic illnesses. By not incorporating this impact on children's health, the current literature could be underestimating the true cost and consequences of smoking during pregnancy, and consequently the cost-effectiveness of cessation interventions during pregnancy.

The impact of the mother's smoking behaviour after pregnancy should also be considered, as this can have detrimental health effects on her offspring. A recent report conducted by the Royal College of Physicians concluded that children's exposure to smoking increased their risk of developing lower respiratory infections, wheezing, asthma, middle ear disease, and bacterial meningitis. [329] The risks associated with breathing problems are also strongly correlated with exposure to maternal smoking, increasing by about 60% for lower respiratory tract illness and 65% for wheezing. As most mothers who quit during pregnancy relapse within one year of giving birth (Chapter 4) and only around 13% of women who smoked throughout pregnancy actually make a quit attempt during the first year after pregnancy [134], maternal smoking behaviour after pregnancy potentially affects many children. Economic models of smoking during pregnancy do need to incorporate the impact of passive smoking on the health of the child. This chapter outlines how the ESIP childhood component attempts to achieve this.

7.3 Objectives

7.3.1 Primary objective:

To estimate the impact of maternal smoking behaviour during and after pregnancy on the health of her infant/child up to the age of 15.

7.3.2 Secondary objectives:

a) To construct a model which includes the relevant morbidities associated with smoking during childhood
b) To estimate the impact of smoking during pregnancy and birth weight on the prevalence of the included morbidities in childhood
c) To estimate the impact of passive smoking on the prevalence of morbidities in childhood
d) To attribute QALYs and healthcare costs to healthy children and sick children during childhood
e) To determine the cost-effectiveness of smoking cessation interventions during pregnancy within a childhood timeframe

7.4 The structure of the Childhood component

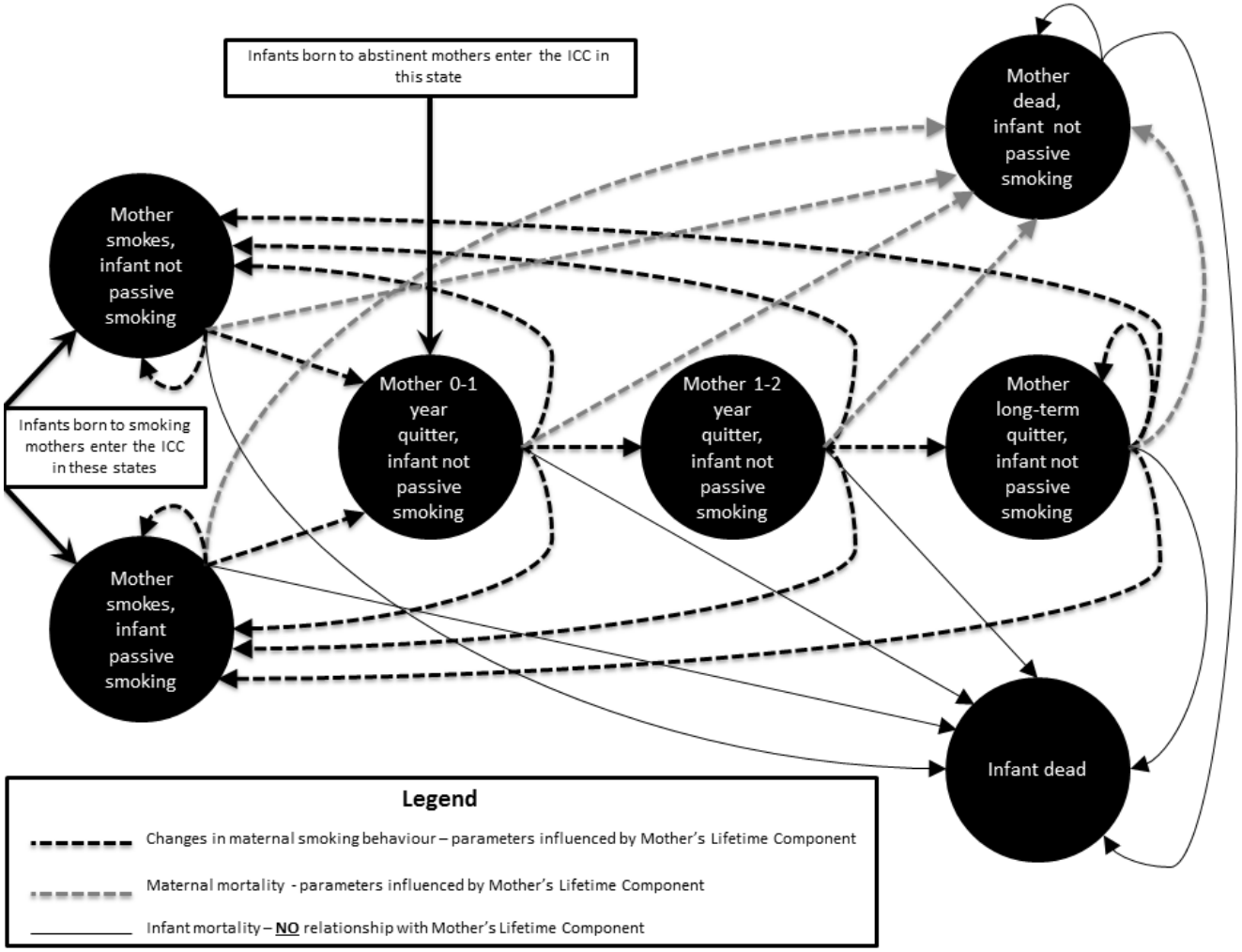
7.4.1 Basic Markov model structure

The 'childhood' component of ESIP had to capture the impacts of infants' passive smoking from exposure to continued maternal smoking, whilst also taking into account smoking during pregnancy. Since the model was primarily concerned with the impacts of cessation interventions for the mother during pregnancy, paternal smoking behaviour was not incorporated into this component. The child's exposure to passive smoking is determined by the mother's smoking behaviour after pregnancy, so the ICC has to reflect the mother's

lifetime component (MLC). Therefore, the Markov structure for the ICC incorporates all the relevant states from the MLC (see Figure 7.2) but with two differences:

1. Mothers who report active smoking, may choose to expose their child or not (e.g. smoke outside the house while the child is inside). Therefore there are two active smoking states instead of one.
2. The addition of a death state for the infant.

Figure 7.2: Markov model structure for the 'childhood' component (ICC) of the ESIP model



The ICC contains seven states linking infants' potential passive smoking exposure to maternal smoking behaviour:

1. Mother smokes, infant exposed to passive smoking
2. Mother smokes; infant not exposed to passive smoking
3. Mother 0-1 year quitter, infant not exposed to passive smoking
4. Mother 1-2 year quitter, infant not exposed to passive smoking
5. Mother long-term quitter, infant not exposed to passive smoking
6. Mother dead, infant not exposed to passive smoking
7. Infant dead

As with the MLC, the states in which the mother makes a quit attempt (0-1 year quitter and 1-2 year quitter) are tunnel states, so infants cannot remain in them for more than one year. The ICC assumes that a mother does not change her active smoking behaviour around her child, i.e. a child cannot transit from exposed to passive smoking to non-exposed if their mother remains an active smoker. For all the states except for infants with dead mothers, there are either four or five possible transitions that an infant can make in each cycle, which are represented in Figure 7.3 to Figure 7.8. The associated transition probability matrix is given in Table 7.1.

Figure 7.3: Possible transitions for children exposed to passive smoking who have a currently smoking mother

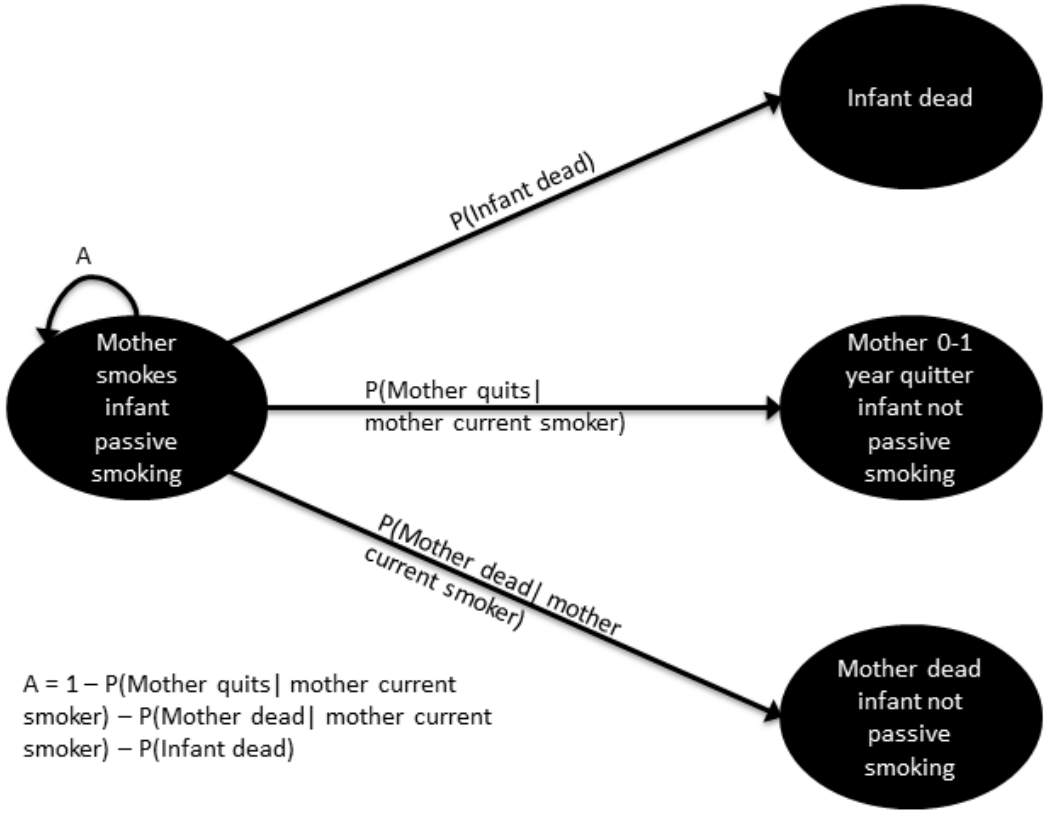


Figure 7.4: Possible transitions for children not exposed to passive smoking who have a currently smoking mother

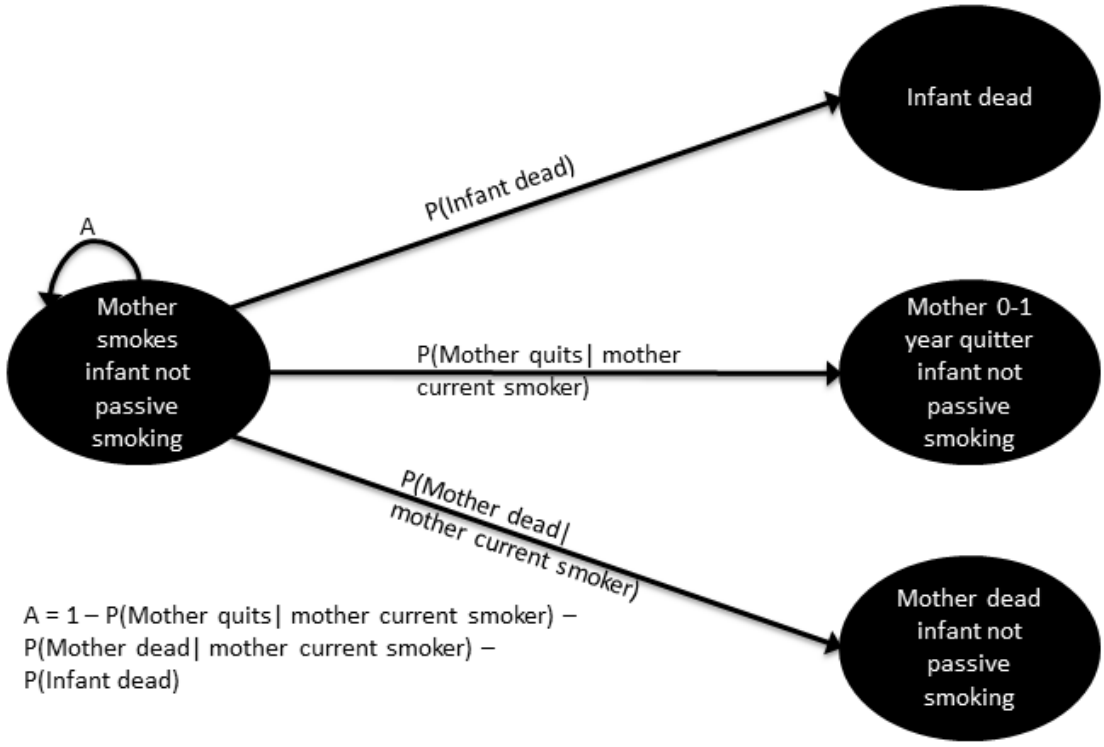


Figure 7.5: Possible transitions for children whose mothers are in the 0-1 year quitter state

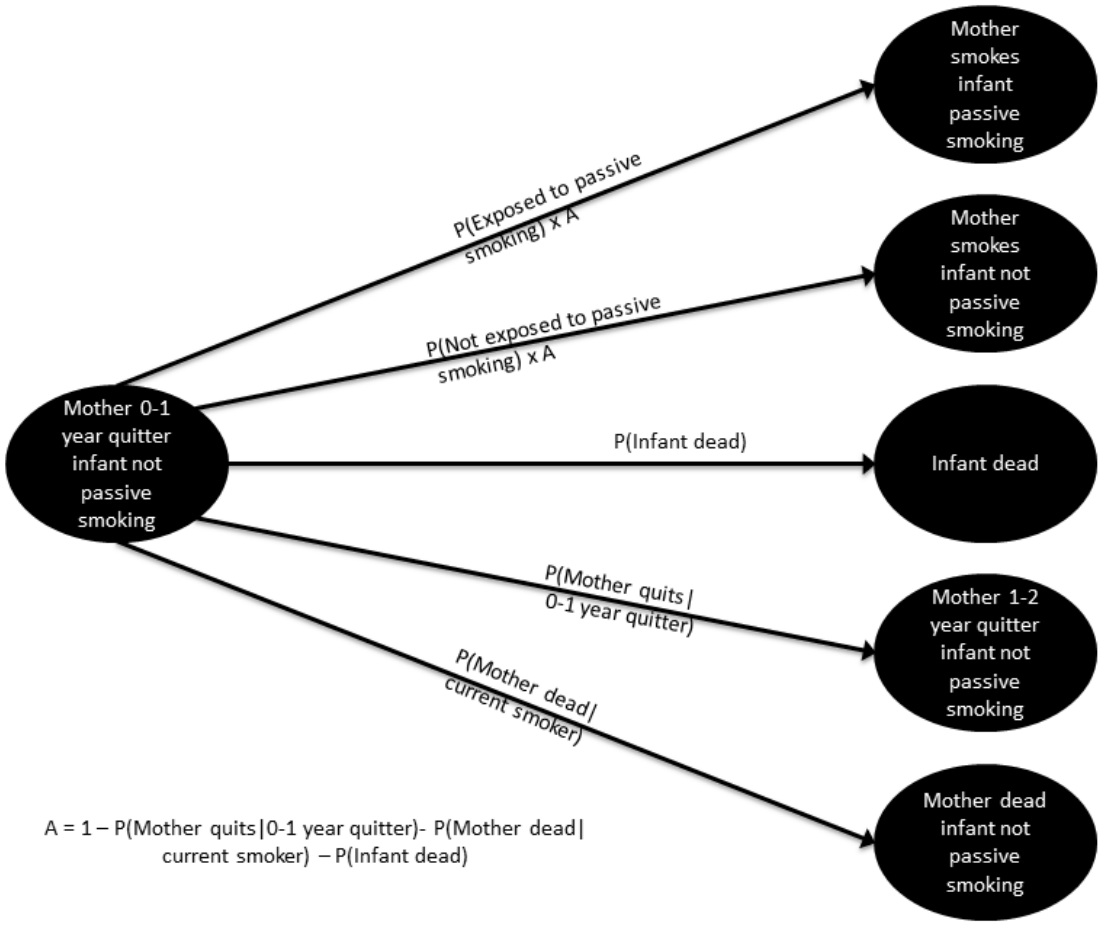


Figure 7.6: Possible transitions for children whose mothers are in the 1-2 year quitter state

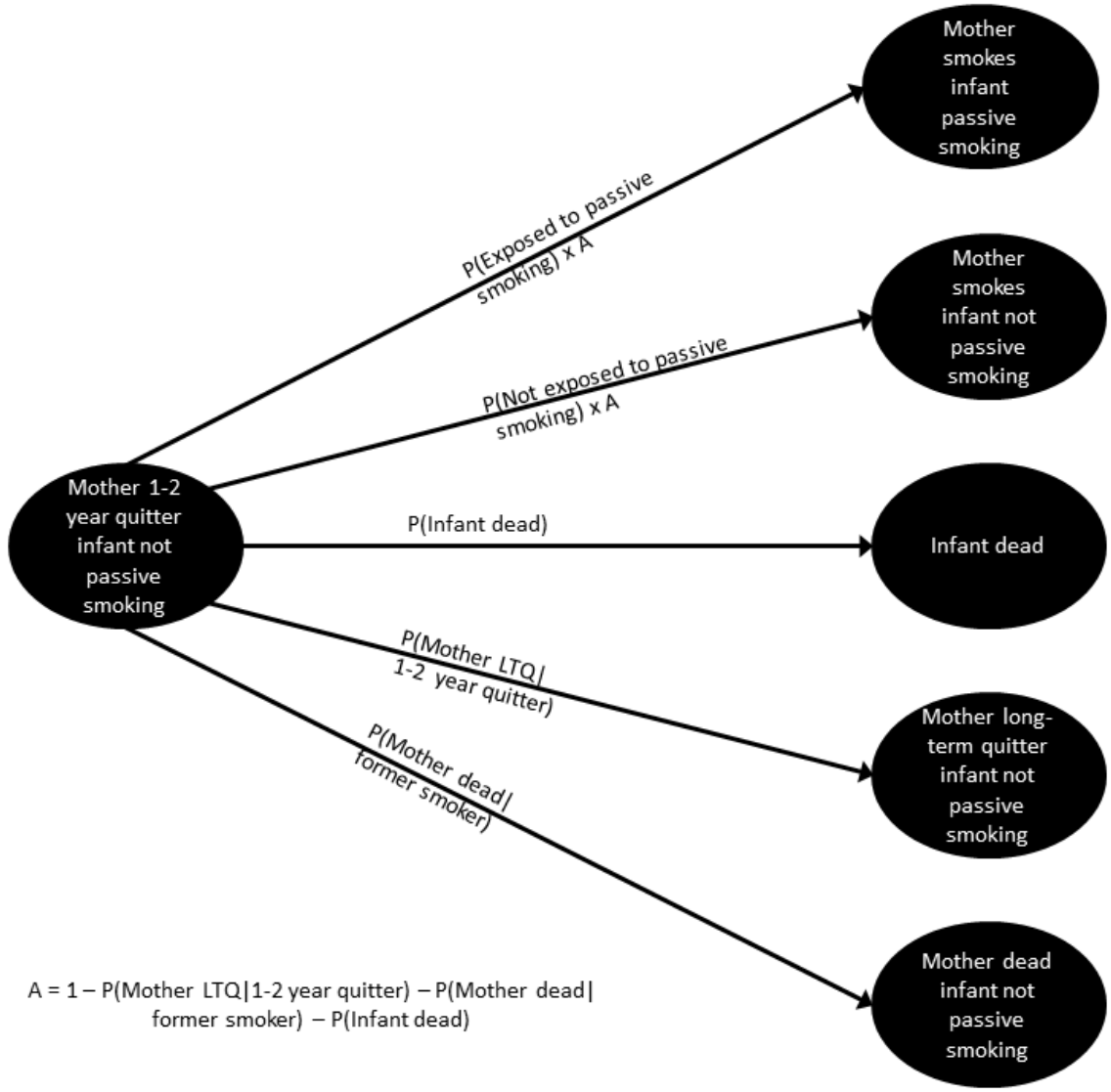


Figure 7.7: Possible transitions for children whose mothers are in the long-term quitter state

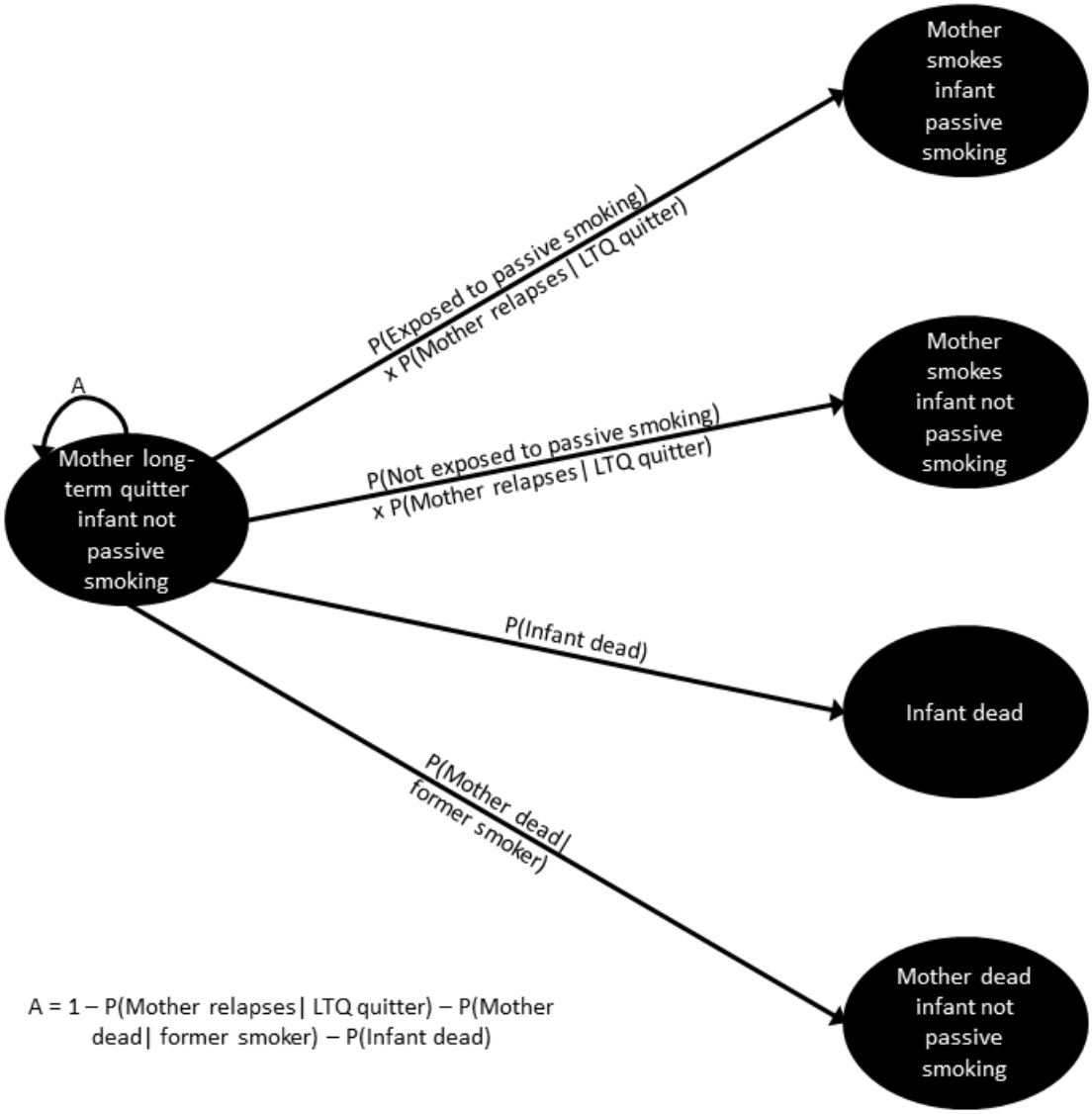


Figure 7.8: Possible transitions for children if their mother is dead.

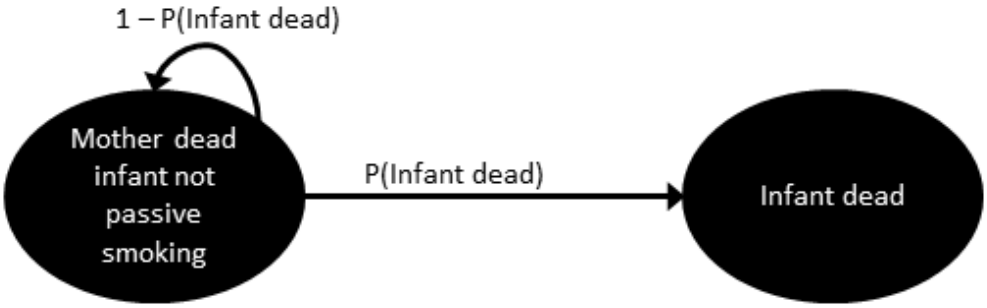


Table 7.1: Transition probability matrix for the ICC

Transition from:	**Transiting to:**						
	Mother smokes infant passive smoking	Mother smokes infant not passive smoking	Mother 0-1 year quitter infant not passive smoking	Mother 1-2 years quitter infant not passive smoking	Mother long-term quitter infant not passive smoking	Mother dead infant not passive smoking	Infant dead
Mother smokes infant passive smoking	$1 - P(MQ_{CS}) - P(MD_{CS}) - P(ID)$	0	$P(MQ_{CS})$	0	0	$P(MD_{CS})$	$P(ID)$
Mother smokes infant not passive smoking	0	$1 - P(MQ_{CS}) - P(MD_{CS}) - P(ID))$	$P(MQ_{CS})$	0	0	$P(MD_{CS})$	$P(ID)$
Mother 0-1 year quitter infant not passive smoking	$P(ES) \times (1 - P(MQ_{1Y}) - P(MD_{CS}) - P(ID))$	$(1 - P(ES)) \times (1 - P(MQ_{1Y}) - P(MD_{CS}) - P(ID))$	0	$P(MQ_{1Y})$	0	$P(MD_{CS})$	$P(ID)$
Mother 1-2 years quitter infant not passive smoking	$P(ES) \times (1 - P(MLTQ) - P(MD_{FS}) - P(ID)$	$(1 - P(ES)) \times (1 - P(MLTQ) - P(MD_{FS}) - P(ID)$	0	0	$P(MLTQ)$	$P(MD_{FS})$	$P(ID)$
Mother long-term quitter infant not	$P(ES) \times P(MR)$	$(1 - P(ES)) \times P(MR)$	0	0	$1 - P(MR) - P(MD_{FS}) - P(ID)$	$P(MD_{FS})$	$P(ID)$

passive smoking							
Mother dead infant not passive smoking	0	0	0	0	0	$1 - P(ID)$	$P(ID)$
Infant dead	0	0	0	0	0	0	1

Where: $\boldsymbol{P(MQ_{CS})}$ is probability (mother quit|current smoker), $\boldsymbol{P(MQ_{1Y})}$ is probability (mother quit longer than one year|quit attempt made last year), $\boldsymbol{P(MLTQ)}$ is probability (mother quit longer than two years|quit longer than one year), $\boldsymbol{P(MR)}$ is probability (mother relapses to smoking|quit longer than two years), $\boldsymbol{P(ES)}$ is probability (infant exposed to passive smoking), $\boldsymbol{P(MD_{CS})}$ is probability (mother dies|current smoker), $\boldsymbol{P(MD_{FS})}$ is probability (mother dies|former smoker), $\boldsymbol{P(ID)}$ is probability (Infant dies)

7.4.2 Starting states for the ICC

As can be seen in Figure 7.1, children whose mothers had smoked throughout pregnancy enter the ICC model in one of the two states representing the mother as a current smoker, allowing for exposure / non-exposure to passive smoking. Children whose mothers had quit smoking during pregnancy enter the ICC model in the state where the mother is a 0-1 year quitter.

7.4.3 Incorporating gender in the ICC

Since there are differences in rates of mortality and childhood related morbidities for both males and females, it was required to split the ICC infant cohort by gender. From the latest birth data for England and Wales, it was estimated that 51% of live born children were male in 2012, and this is consistent with other years going as far back as 1839. [330] Therefore, the modelling was initiated with 51% of children born alive in the within-pregnancy component assumed male. It was however assumed that LBW did not vary with gender; therefore 51% of LBW infants were male.

7.4.4 The proportion of infants exposed to passive smoking

In England, an estimated 23% of female smokers report smoking at home with children present. [134] Therefore, it is assumed that 23% of infants born with an actively smoking mother enter the exposed to passive smoking state, while the remaining 77% entered the not exposed to passive smoking state. This distribution was applied throughout all cycles of ICC to any infant in which the mother relapsed to smoking.

7.4.5 Cycle length

To match the maternal lifetime component, the ICC adopted cycles of one year in length. The model ran for 15 cycles, from age 0 to age 15 years, so the first cycle represented the estimates at age 1. 15 cycles were chosen as the final age of the model, as up to age 15 the

child can be heavily dependent on their mother. At age 16, it is assumed the child is no longer dependent on their mother, and hence is divorced from the influences of maternal smoking behaviour. Furthermore, UK national data reports smoking prevalence from age 16 onwards [134], suggesting that a separate smoking behaviour model for the infant may be more appropriate from age 16 years and above. The smoking behaviour of the child beyond age 16 years and the associated impacts on HRQoL are beyond the scope of the ICC and this thesis.

7.5 Parameterisation of transition probabilities associated with maternal smoking behaviour

The ICC attempts to capture the impacts of the mother's smoking behaviour on the health of the child, thus the ICC uses the same parameters for the transition probabilities as the MLC. Therefore, the two models are linked such that the values associated with the mother's smoking behaviour (probability of quit attempt, probability of relapse, probability of death of the mother due to active smoking) are directly reproduced in the ICC, including the pregnancy-related two year postpartum values. This can be seen in Figure 7.2, where the transition pathways influenced by maternal smoking behaviour in the MLC are represented by the black dashed arrows, and the transition pathways influenced by maternal mortality in the MLC are represented by the grey dashed arrows. The thin black arrows represent transition pathways which are not influenced by the MLC. It should be noted that although the probability of relapse comes directly from the MLC, it is adjusted to take into account the proportion of mothers who expose their child to passive smoking. Since the determinants of these parameters were given in detail in Chapter 6 , these will not be reproduced here; instead focus is placed on the additional values specific to the infant.

7.6 Incorporating infant mortality

The transition probability for death was taken from ONS Cohort Life Tables, Table B1 [313] which, for children born between 1981 to 2012, reports mortality probabilities for males and females in the UK from birth to 100 years old, and projections for children born up to 2062. It was assumed that passive smoking had no impact on children's mortality, although

LBW increased the risk of mortality in childhood. The mortality probabilities were adjusted using the odds ratios in Table 7.2.

Table 7.2: Odds ratios for increased risk of mortality during childhood associated with LBW

Age (years)	Odds ratio	95% confidence interval	
1-4	2.2	1.9	2.5
5-9	1.7	1.3	2.1
10-14	1.5	1.1	1.9
15-19	0.9	0.7	1.1
Source: Table 4, Li et al, 2003. **[331]**			

Due to the mortality data being used in the ICC, it was not possible to break down mortality in the first year to capture the impact of SIDS. Therefore, the ICC does not capture the impact of smoking during pregnancy on the increased rate of SIDS; however, the all-cause mortality rates used by the ICC will have incorporated a death rate for SIDS for both smoking and non-smoking mothers in the calculations of predicted mortality.

7.7 Incorporating smoking related smoking morbidities

As identified in Chapter 2 of this thesis, only respiratory illness was identified as having a causal link with smoking in pregnancy. Respiratory illness covers many diseases, including asthma; lower respiratory tract infections; and upper respiratory tract infections. We chose to focus the impacts of asthma on the infant during childhood since it is one of the most common childhood diseases; it has a large burden in terms of healthcare cost; and there was a strong link between asthma and exposure to smoking both within and after pregnancy. [329, 332]. Table 7.3 reports its prevalence in the UK by age and gender.

Table 7.3: Prevalence of asthma up to age 19

Age (years)	Males (%)	Females (%)
0-4	2.29	1.36
5-9	11.41	7.88
10-14	19.18	14.11
15-19	22.34	18.27
Source: Public Health England analysis **[333]**		

Asthma in childhood has also been linked with LBW. [334] Since the ICC calculated the number of infants who were born with LBW, it was decided to incorporate this impact into the prevalence of asthma independently to the impacts of smoking. Table 7.4 reports the odds ratios for the various impacts on the increased risk of asthma.

Table 7.4: Odds ratios for increased risk of childhood asthma

Condition		Pooled odds ratio	95% confidence interval		Source
LBW		1.28	1.09	1.50	Mu et al [334]
Child aged 0 - 2 years	Mother smokes during pregnancy	1.85	1.35	2.53	Burke et al [70]
	Passive smoking from mother	2.47	0.65	9.39	Burke et al [70]
Child aged 3 - 4 years	Mother smokes during pregnancy	1.30	0.88	1.92	Burke et al [70]
	Passive smoking from mother	1.05	0.88	1.25	Burke et al [70]
Child aged 5 - 18 years	Mother smokes during pregnancy	1.23	1.12	1.36	Burke et al [70]
	Passive smoking from mother	1.20	0.98	1.44	Burke et al [70]

Using the methods already outlined in Chapter 5, the prevalence of asthma was calculated for LBW and normal birth weight children with the following exposures to smoking:

- both during pregnancy and during childhood;
- during pregnancy but not during childhood
- childhood but not pregnancy

No data were available on how quickly the risk of asthma changed after the mother had quit smoking, therefore the increased risk of asthma from passive smoking was only applied to those children who were subject to passive smoking while their mother is a current smoker. If the mother was not exposing her child to passive smoking, the risk of asthma to that child was assumed to be equal to those whose mothers were former smokers. The prevalence of asthma was applied in the same manner as that of smoking-related morbidities for women in the MLC; with the estimated number of asthmatic children being dependent on the smoking behaviour of mothers[43].

7.8 Health related quality of life

Chapter 2 identified several studies which reported utility values for children suffering from asthma. The largest study (Carroll et al) reported utility values for 4,016 children under the age of 18 years based on parents' views. This study used the standard gamble technique to elicit utility values for asthma and perfect health. [163] Three possible utility values were estimated for children with mild intermittent, mild persistent and severe persistent asthma. It was assumed that since the utility values for mild intermittent and mild persistent asthma were almost the same, and since the model assumes that every child who developed asthma received treatment for it, the mild persistent asthma utility value was appropriate. These utility values were used to weight the life year, generating QALYs, and discounted by 3.5% per annum, as recommended by NICE guidance. [36] The values used in the ICC are reported in Table 7.5.

[43] Please note: due to constraints in this thesis, these values have not been reproduced in this document. However, the prevalence values used in ESIP can be found under the "Childhood asthma" tab in the ESIP spreadsheet.

Table 7.5: Utility values used in the childhood component of the ESIP model

Condition	Mean value	Standard deviation
Perfect health	1	-
Asthma	0.9	0.18
Source: Table III Carroll et al. **[163]**		

7.9 Healthcare costs of morbidities

It was assumed there would be a treatment cost associated with childhood asthma. In keeping with the work performed in Chapter 6, the direct cost of healthcare for asthma was identified from the economic burden of disease literature. This was estimated at £1,565.27 per patient[44]. [320] The cost was estimated from a study which included both children and adult treatment, therefore appeared to be an appropriate estimate. This cost was applied per annum to all children who were estimated by the model as having asthma during childhood in each cycle.

It was also assumed that there would be an NHS related cost attributable to death during childhood, which is consistent with previous work. [4] From Chapter 5, the cost of a cardiac event was used as a proxy, estimated to have a weighted mean cost of £1,379.02 and a quartile range of £799.89. [298] This cost relates to both children and adults, since it is not possible to split the NHS reference cost data for paediatric events. This cost was applied to all children who died in a cycle; all costs accrued were discounted at 3.5% per annum. [36]

7.10 Discussion

This chapter has described the childhood component (ICC) of ESIP. The ICC estimates the number of children who suffer from asthma associated with passive smoking, while taking into account the mothers' smoking during pregnancy and child's birth weight, and

[44] Direct cost of healthcare: EUR 1950, converted 8/9/2014, 1 EUR = £0.8026, http://www.currency.me.uk/convert/eur/gbp

attributes relevant utilities and health costs to these children. This will allow the economic impact of maternal smoking during pregnancy and afterwards on infants and children to be estimated.

7.10.1 Strengths of the childhood component

There are several key areas where ESIP has the advantage over other models. The ICC is directly linked with the MLC, so it is possible to estimate the impact of the mother's smoking behaviour after pregnancy on the health of her child. While there have been other economic models which have considered the 'within-pregnancy' aspect of the link between the mother's smoking behaviour and health consequences on the infant, until now no model in this topic area has attempted to link post-pregnancy smoking behaviour and its consequences on the health and healthcare costs for the infant. By omitting the costs and consequences for the infant during childhood, the previous economic literature has missed the negative health consequences that can occur due to active smoking during childhood. This would suggest that the previous literature is producing inaccurate estimates of the cost-effectiveness of smoking cessation during pregnancy.

Only two economic models have attempted to estimate the longer term impacts of smoking during pregnancy on children's health. One model did not take into account any smoking related morbidities associated with childhood. [139] The other model incorporated the impact of smoking during pregnancy on the prevalence of asthma and otitis media, as well as the impact of LBW on the HRQoL of the infant. [190] As discussed in Section 2.5.3, the author found no evidence of a causal link with otitis media and therefore the inclusion could be viewed as a misspecification.

It could be argued that the ICC is double-counting the impact of asthma, since it includes the links with asthma from exposure to smoking during pregnancy and exposure to passive smoking. Conversely, the author would argue that an infant exposed to smoking both within the womb and during childhood would have a greater risk of developing asthma compared to a child who is only exposed to either smoking within-pregnancy or during childhood. Thus, to control for this, the author first adjusted the prevalence of asthma to take into account the exposure to smoking within-pregnancy, then further adjusted the prevalence rates to take into account whether the child is exposed to passive smoking.

Using this approach, the ICC should have prevented any double-counting. However, if there is double-counting, then this would suggest that the ICC is overestimating the number of infants who develop childhood asthma, and thus overestimating the benefits from cessation, suggesting that the ICERs the ICC estimates are too low and should be higher. One approach to determine if this is the case is to use the ICC to replicate a cohort of infants and compare the prevalence of asthma within the ICC estimates with that of the cohort, although this is beyond the scope of this thesis.

The birth weight of the child could be an important aspect, especially as it is associated with several morbidities and increased mortality during childhood. [331, 334] The ICC is also the first model in this topic area which incorporates the impact of LBW on increased morbidity and mortality. Since smoking during pregnancy can also influence birth weight, by building Markov chains contingent on the child's birth weight, the ICC captures both the direct impacts of smoking on children and the potential longer term impact of LBW on subsequent health. This suggests that the ICC is a more accurate representation of the health impacts of smoking during pregnancy on childhood health of the infant, giving accurate estimates of healthcare costs and health consequences.

7.10.2 Limitations of the childhood component of the ESIP model

Nonetheless, there are limitations associated with the ICC. The ICC only includes the impacts of passive smoking related to the mother. For example, it is likely that exposure to passive smoking from any adult that shares a home with a child will heighten morbidity risks, especially if it is the mother's partner/child's father. However, the ICC is constructed to estimate the impacts of cessation interventions during pregnancy, which are delivered exclusively to the mother. Therefore, it could be argued that we are not interested in the impact of other adults' smoking behaviour, as this is external to the primary objective of the cessation intervention for the mother. Additionally, the exposure to smoking is likely to be higher from the mother than it is from any other adult, including the father/partner. In the Royal College of General Physicians report, Passive smoking and children [329], it was estimated that children whose father only smoked had cotinine levels that were 2.9 times higher than children with non-smoking parents; meanwhile children where only the mother smoked had 6.4 times higher levels of cotinine concentration. This would suggest that the

greatest exposure from passive smoking comes from the mother, and therefore the ICC is likely to be capturing the biggest impact of smoking behaviour after pregnancy.

The ICC assumes singleton pregnancies and does not take multiple births into account. In 2011, out of the 723,913 live births that occurred in England and Wales, 22,934 (or approximately 3%) were multiple births. [335] If a mother gives birth to more than one child, then the healthcare costs of passive smoking would be expected to increase as the mother's smoking behaviour now impacts on two or more children, rather than one. This is not captured in the ICC, as one of the assumptions of the model is that the pregnancies are singleton. If this assumption is deemed unrealistic, it may be possible to model a cohort of maternities with multiple births by doubling the number of infants in the cohort, e.g. 100 mothers give birth to 200 infants. However, multiple births are a relatively infrequent occurrence, and therefore perhaps not a major concern of decision makers. Furthermore, if a cessation intervention proved to be cost-effective for a single child, it is also highly likely that having more than one child will not change the cost-effectiveness, making an analysis of multiple births redundant.

The ICC also doesn't consider any subsequent births. This means that the model only estimates the impacts associated with the one infant, and does not take into account the impact of the mother's smoking behaviour on any other children. This would suggest that the ICC is potentially underestimating the costs associated with smoking behaviour and the impact on the child. Furthermore, there may be changes in the mother's smoking behaviour due to the additional child, which would have an impact on the health consequences for the infant modelled in the ICC. However, the ICC adopts a one mother-one child approach. Seeking to extend the model to address the implications of maternal smoking if younger siblings enter the family later in time would not be relevant to the current investigation, and is therefore excludable from the ICC.

Another limitation is that the ICC does not directly capture the impact of smoking during pregnancy on the risk of the infant suffering from SIDS. Primarily, this was because of the limitations of the available data. Although the all-cause mortality rate incorporates some measure of SIDS, the ICC is unable to differentiate between SIDS and other causes of death in the first year. An implication of this is that the ICC is not capturing the benefits of cessation during pregnancy on the impact on the risk of SIDS, therefore underestimating

the cost-effectiveness of cessation interventions. Nevertheless, the incidence of SIDS is generally very low, and since the ICC is already attributing a healthcare cost of death, the incorporation of SIDS is unlikely to have a significant impact on its overall results. However, consideration should be given to a possible expansion of the ICC to differentiate SIDS from other mortality in the first year.

An additional limitation is that the ICC only includes the impacts of smoking both within- and post-pregnancy on the rates of asthma amongst the cohort of infants. As Chapter 2 of this thesis demonstrated, we only found of a causal link between smoking and two conditions affecting the health of the infant: respiratory illness and congenital anomalies, and congenital anomalies were excluded on the basis that they occurred very infrequently. The term 'respiratory illness' covers several conditions, which include lower respiratory tract infections as well as asthma, which have been demonstrated to have a link with both smoking during pregnancy and passive smoking. [336] Asthma was focused upon as it was one of the most common respiratory diseases, and has a large health burden, as stated in Section 7.7. However, it could be that focusing on asthma is excluding the other respiratory diseases, such as lower respiratory tract infection. These diseases could have a substantial economic burden in terms of healthcare costs and quality of life lost. [337] Their omission from the ICC suggests that it could be underestimating the healthcare costs attributed to smoking, as well as the benefits to be gained from cessation during pregnancy in terms of quality of life for the infant. This in turn suggests that the ICERs estimated by the ICC are too high, and that the true cost-effectiveness of cessation interventions could be lower. However, the author would argue that the inclusion of asthma is likely to capture most of the burden of childhood respiratory diseases, although the inclusion of other respiratory diseases as well as other childhood diseases could be included in any future work in developing the ESIP model.

Another consideration is that the ICC does not take into account other impacts of LBW other than the increased prevalence of asthma amongst these children as well as the increased mortality (see Sections 7.6 and 7.7). There is some evidence that the quality of life of infants born with LBW is lower throughout their childhood compared to infants born with normal weight [338-340], although a systematic review suggests that the greatest impact on the quality of life occurs in the first few years of life and diminishes over time. [341] All this would suggest that the ICC should have put a lower utility value on infants

that are assigned to enter the LBW Markovs of the ICC compared to infants born with normal birth weight. The omission of the lower utility values for LBW infants suggest that the ICC is underestimating the benefits of cessation since cessation leads to a reduction in the number of LBW infants. This implies that the ICER estimates are higher than the reality, and hence ESIP may be underestimating the cost-effectiveness and value for money of cessation. However, it would be relatively easy to introduce a lower utility weight amongst LBW infants to correct this issue, should future researchers wish to do so.

One final limitation is that the ICC only takes into account passive smoking impacts and there may be others that are not taken into account. For example, smoking is heavily linked with being in a lower socioeconomic status [342], and mortality and morbidity have been demonstrated to be higher in individuals who are lower socioeconomic status. [343] Furthermore, childhood asthma has been demonstrated as being linked with socioeconomic status [344], and since asthma is included in the ICC it would seem that socioeconomic status warrants inclusion. The omission of this impact could suggest that the ICC is not producing accurate estimates as to the number of infants exposed to morbidities and premature mortality within the model, since it is likely that a greater percentage of the cohort will of be low, rather than high, socioeconomic status, and therefore will have higher rates of morbidity and mortality than the higher status infants. This in turn would suggest that the ICER estimates are too high and ESIP is underestimating the cost-effectiveness of cessation interventions. However, it should be noted that if a cessation intervention was delivered as part of the NHS, women would have access to these interventions regardless of their socioeconomic status, and since the ICC uses national prevalence rates, the policy maker could be argued as interested in knowing the cost-effectiveness of cessation interventions to the average pregnant women, which ESIP currently calculates. One possible avenue of future work could be to perform a sub-group analysis of pregnant women by socioeconomic status to determine whether cessation interventions are more cost-effective for those who are of lower socioeconomic status.

7.10.3 The childhood component in the context of current literature

The model constructed by Taylor did not include impacts from smoking-related childhood morbidities or attempt any linkages between the mothers' smoking behaviours and childhood impacts. [139] Instead, it simply estimated discounted QALYs for children born to

smoking and abstinent mothers, and assumed that those born to smokers had a slightly higher mortality rate under five years of age and higher costs due to increased healthcare. Estimates used were that, by age 79, a child born to a smoking mother would lose 0.02 QALYs and cost £371 more than the child of an abstinent one. Because the ICC is so different to this model, it is difficult to make direct comparisons. However, the most important improvement the ICC has over this study is that it incorporates the impact of the mother's smoking behaviour after pregnancy. This would suggest that the ICC is producing better estimates of the impact of smoking after pregnancy on the health and healthcare costs associated with the child, and more precise estimates of the cost-effectiveness of cessation interventions during pregnancy.

More recently, a model by Mallender et al took into account the impact of smoking during pregnancy on the prevalence of otitis media/ asthma on the HRQoL of the infant; this model also took into account some of the impacts of LBW. [190] This was done using a similar approach to the ICC, by calculating the prevalence of asthma amongst infants born to smoking and non-smoking mothers, as well as the number of infants born with LBW and NBW. The HRQoL estimates were not generated by Markov chains, but by extrapolating discounted QALYs over an assumed lifetime of 100 years. Furthermore, it treated asthma as a mutually exclusive morbidity to birth weight, which we know not to be the case. [334] In addition, the model excluded the impact of passive smoking, arguing that it was necessary to take into account passive smoking relating to the mother's partner. The ICC is an improvement because it takes into account 1) the dependency of asthma on birth weight and 2) that passive smoking has an impact directly on the child's health. The ICC does not include the partner's smoking, however, the greatest impact on health and increased risk of asthma comes from exposure to maternal passive smoking. [70, 329] Therefore the ICC is capturing what could be considered the most important aspect of passive smoking impacts. Conversely to the inclusion of otitis media in the model by Mallender et al, we identified no strong evidence of a causal association with smoking during pregnancy; however, if such a relationship did exist, a future improvement of the ICC could introduce this impact.

7.10.4 Exposure to passive smoking in the home

The 23% estimate as to the number of children who are exposed to smoke comes from Table 3.17 in the latest Statistics on Smoking: England report. [134] However, this value is

likely to change considerably. For example, in the US, the proportion of non-smokers who had levels of cotinine in their bodies (which suggested they had been exposed to second-hand smoke) has decreased from 87.9% in 1988 to 25.3% in 2012. [345, 346] This decrease has been attributed to the increase in public health awareness and interventions attempting to curb the exposure to second-hand smoke. [346] However, it is still estimated that two in five children are exposed to regular passive smoking in the US [346], suggesting that the proportion is around 40%. In the UK, there have been further public health interventions, such as the 2003 restrictions of smoking in day care settings and the smoke-free workplaces and enclosed public places smoking ban that was introduced in July 2007. It has been suggested that such public health interventions reduced children's exposure to smoking, with a study in Scotland suggesting that the percentage of children exposed to second-hand smoke fell by 39% since the introduction of smoke-free legislation. [347] However, recent work has suggested that the proportion of children exposed to second hand smoke is much higher than the 23% used in the ICC. In 2012, it was estimated that around 67% of pupils were exposed to any second-hand smoke, with 55% exposed at other people's homes and 43% exposed in their own home, while 26% were exposed in their family car. [348] However, it has been suggested that these values will decrease, especially with the forthcoming legislation regarding the banning of smoking in cars. [349] These public health interventions are likely to draw down the proportion of children exposed to passive smoking, and there is evidence that the introduction of previous smoke-free legislation has impacts on the prevalence of passive smoking at home, since the percentage of smoke-free homes increased from 61% in 2006 to 67% after the 2007 smoke free legislation. [350] Therefore, the October 2015 legislation banning smoking from cars is likely to have a similar impact. [349]

The higher rates suggest that there is a great deal of uncertainty to be associated with the proportion of infants exposed to passive smoking. If the higher rates are correct, then the ICC is underestimating the number of children exposed to passive smoking; and hence underestimating the healthcare costs associated with passive smoking and the benefits to be gained from smoking cessation during pregnancy (and thereby preventing exposure to passive smoking). This would also suggest that the ICER estimates are too high for cessation interventions, and that ESIP is undervaluing the value for money of cessation interventions. However, because of the large degree of uncertainty associated with the proportion of

smoking at home, this parameter would certainly be an important consideration for both a one-way deterministic sensitivity analysis as well as for inclusion in a probabilistic sensitivity analysis.

7.10.5 Potential future extensions of the ICC

One potential area for future improvement would be to develop the evidence base around the childhood morbidities associated with smoking during pregnancy and/or passive smoking. Chapter 2 actually identified eight conditions that had some evidence linked with smoking during pregnancy; however, only respiratory illness was assessed to have a likely causal link. Certainly the relationship between smoking and pregnancy seemed unclear for some conditions. A report by the Royal College of Physicians suggested that passive smoking led to increased risks of several other conditions, including respiratory infections other than asthma, and bacterial meningitis. [329] This thesis primarily focused on the impacts of smoking during pregnancy, and as such the evidence associated with passive smoking and infant health has not been evaluated to the same degree. It could be argued that any childhood model containing passive smoking should consider all associated diseases. It would seem appropriate that a future extension to the ICC would be to evaluate the evidence for passive smoking and childhood diseases to ensure that it contains all relevant morbidities. Should further research identify one of the morbidities associated with smoking during pregnancy as having a causal link, it would be deemed appropriate for the ICC to include it. Furthermore, it would also be prudent to evaluate the current literature on morbidities associated with passive smoking to identify those with a causal link and thus ensure inclusion of all relevant smoking related morbidities.

Another consideration is the expansion of the ICC to differentiate SIDS from other mortalities in the first year. As discussed in Section 7.10.2, although some measure of SIDS is incorporated in the all-cause mortality rate, limitations to the current data have prevented its inclusion as a specific cause of death. Although its incidence is generally low, it may be an improvement to the ICC to capture its prevalence separately to other causes of death, to ensure the benefits of cessation during pregnancy on reducing the risk of SIDS is reflected. Therefore its inclusion in an expansion of the ICC, given an improvement in the available data, could be seen as increasing the accuracy of the model.

Another avenue for possible research is better utility data. Currently, the ICC assumes that a healthy infant has a utility of 1, and asthmatic infant has a utility of 0.9. The utility of 1 for the healthy infant might been seen as unrealistic; however, there is very little research reporting utilities for children. One study estimated that the utility for school children aged 11 years and older as 0.9 for healthy infants, which is very similar to the value used for asthmatic children in the ICC. [351] There may be almost no difference in utilities between a child with asthma and perfect health, although this would seem unlikely. There is also no utility data exploring differences in utilities by gender. Further research either undertaking improved utility estimates in children or identifying more reliable utility sources could be beneficial to the ICC.

One possible limitation that could also be addressed is the inclusion of passive smoking from the mother's partner. However, as has been discussed in the above section, the majority of the impact comes from maternal smoking and therefore it is unlikely that it would make a significant difference to the output of the model. Consideration should also be given to the added level of complexity which this would introduce, making the ICC very difficult to evaluate and analyse.

7.11 **Summary**

The ESIP childhood component attempts to capture the impact of the mother's smoking behaviour, both during pregnancy and afterwards, on health and healthcare costs for the child up to and including the age of 15 years. The structure of the ICC allows direct links to the MLC, and estimates the number of infants exposed to passive smoking dependent on their mother's smoking behaviour. Although there are several limitations associated with the ICC, this is the first economic model to link the mother and her child together in this manner. It is novel in that it includes smoking-related childhood morbidities.

Chapter 8: The ESIP model: How ESIP brings four components together to model the impacts of smoking and smoking cessation during pregnancy

8.1 Introduction

Chapters 5, 6, and 7 outlined the four components of the ESIP model in depth. Although these are referred to as 'components', they are four standalone economic models; two within-pregnancy and two longer term, representing after pregnancy. ESIP combines these into a series of linked models, which give as comprehensive a picture as possible of the economic impacts of smoking during pregnancy, enabling the impacts of maternal smoking both during and after pregnancy to be modelled directly on the health and healthcare costs of the infant. The author will present how ESIP was constructed within a software package, and give guidance on how a user can evaluate a cessation intervention using ESIP, producing the results for both a deterministic and probabilistic analyses.

8.2 Aims and objectives

8.2.1 Primary aim:

To describe the construction and use of ESIP

8.2.2 Secondary objectives:

1. Describe how the four ESIP components (MWPC, MLC, IWPC, and ICC) are linked
2. Define how ESIP captures the differences in smoking behaviour between control and intervention groups
3. Describe how ESIP determines whether an intervention is cost-effective or not
4. Explain how ESIP was expanded to be probabilistic
5. Illustrate how ESIP was constructed in a computer package

8.3 **Combining the four components**

8.3.1 Assumptions in ESIP

The following assumptions about the cohort of mothers and infants are required for ESIP to function:

1. All women who enter the ESIP model are actively smoking at conception
2. All pregnancies included in the ESIP are singleton
3. All infants considered in the model are born to women who have been included in earlier components of ESIP
4. There is no impact from included complications of pregnancy on mothers after pregnancy
5. The chance of an adverse birth outcome does not vary with infant gender

8.3.2 Brief summary of the four components

The four components are summarised as follows:

- Mother within-pregnancy (MWPC, see Chapter 5): Models the impacts of smoking during pregnancy on the following smoking-related pregnancy complications: ectopic pregnancy, miscarriage, abruption, previa and pre-eclampsia. Also captures the impact of foetal loss on the HRQoL of the mother.
- Infant within-pregnancy (IWPC, see Chapter 5): Models the impact of maternal smoking behaviour on infant adverse pregnancy outcomes, including foetal loss (ectopic, miscarriage, stillbirth), LBW and premature birth.
- Mother Lifetime (MLC, see Chapter 6): Models smoking behaviour after pregnancy on maternal risks of four chronic diseases (CHD, COPD, LC and stroke).
- Infant Childhood (ICC, see Chapter 7): Models the impact of maternal smoking behaviour on the health of the child in relation to asthma.

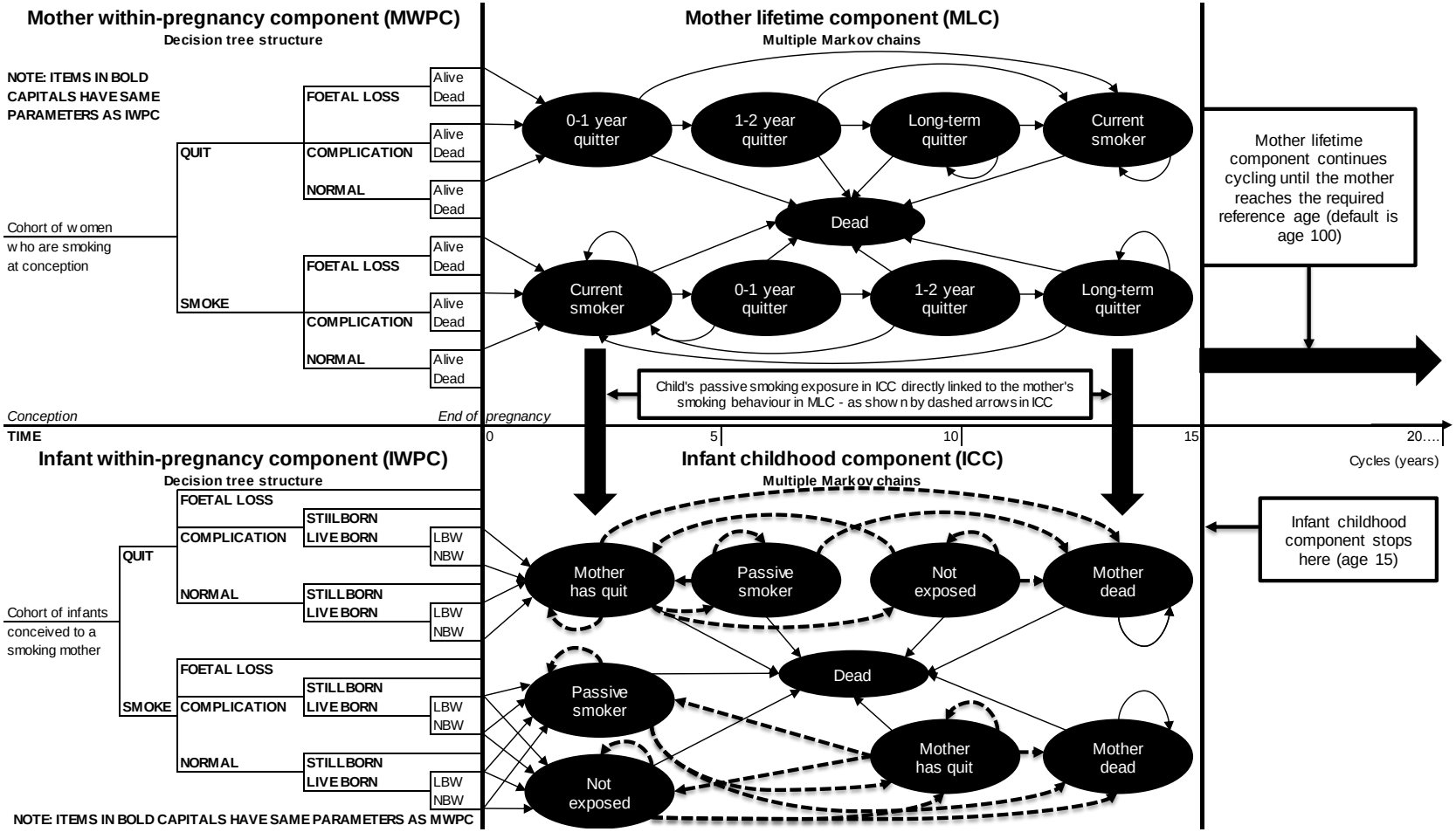
8.3.3 Brief summary of components' links

At the beginning of ESIP there is a cohort of women smoking at conception and an associated cohort of infants carried by and subsequently born to them. ESIP is a two stage process whereby the cohorts initially flow through the respective 'within-pregnancy' components (MWPC and IWPC). Outputs from these are fed into a series of Markov chains representing maternal lifetime (MLC) and infant childhood (ICC). Within ESIP there are two types of links between the four components:

- The influence link: This occurs where the IWPC shares parameters with the MWPC and also where the ICC shares parameters with the MLC; these links represent the impact of the mother's smoking behaviour on her offspring.
- The flow link: This describes the sequential nature of ESIP components, which allows the lifetime components to take into account the within-pregnancy behaviour / outcomes. For example, the cohort of women must first pass through MWPC (i.e. pregnancy) before MLC (i.e. the rest of their lifetimes). A similar 'flow link' occurs between IWPC and ICC.

Figure 8.1 gives a simplified overall structure, highlighting the two types of links, and the following sections will describe how ESIP was constructed in greater detail. Figure 8.1 depicts how the influence of maternal smoking behaviours in MWPC impact on the infant through the IWPC having the same estimate parameters (highlighted in bold capitals in Figure 8.1), as discussed in Chapter 5. The impact of maternal smoking post-pregnancy on the infant's exposure to passive smoking is captured by the ICC sharing the same parameters as the MLC, as described in Chapter 7 and also shown in Figure 8.1.

Figure 8.1: Simplified overall structure of ESIP with all four components (MWPC, IWPC, MLC, and ICC), demonstrating how members of both cohorts flow through ESIP, and the influence links between the mother and her offspring



8.3.4 Linking the maternal within-pregnancy and maternal lifetime components

The first stage for the maternal cohort is to flow into the MWPC, which estimates the costs and HRQoL that the women receive during pregnancy. Some of the output from the MWPC at the end of pregnancy includes the number of:

- Women who quit and are alive
- Women who quit and die during pregnancy
- Women who smoke and are alive
- Women who smoke and die during pregnancy

These outputs then form the cohort sizes that enter the Markov chains in the MLC. In Figure 8.1, women who quit and are alive (regardless of within-pregnancy complications) enter an MLC Markov chain in the 0-1 year quitter state, representing the fact that they are making a quit attempt but have done so for less than a year. Women who smoke and are alive enter another series of MLC Markov chains in the current smoker state. For both quitters and smokers, the estimated healthcare costs and HRQoL form sunk costs attributed in cycle 0 of the MLC. A sunk cost is one that has already been incurred and cannot be recovered. To enter the MLC, any pregnant woman has to have flowed through the MWPC. The costs and HRQoL generated by the MWPC can be seen as unrecoverable in the MLC (i.e. they have occurred before the MLC model), and thus can be treated as a sunk cost. The MLC then runs the necessary number of cycles to a lifetime horizon when the cohort numbers are reduced to zero.

8.3.5 Linking the infant within-pregnancy and lifetime components

For the cohort of infants, the first stage of ESIP is to process through the IWPC At the end of pregnancy, some of the IWPC output includes the number of:

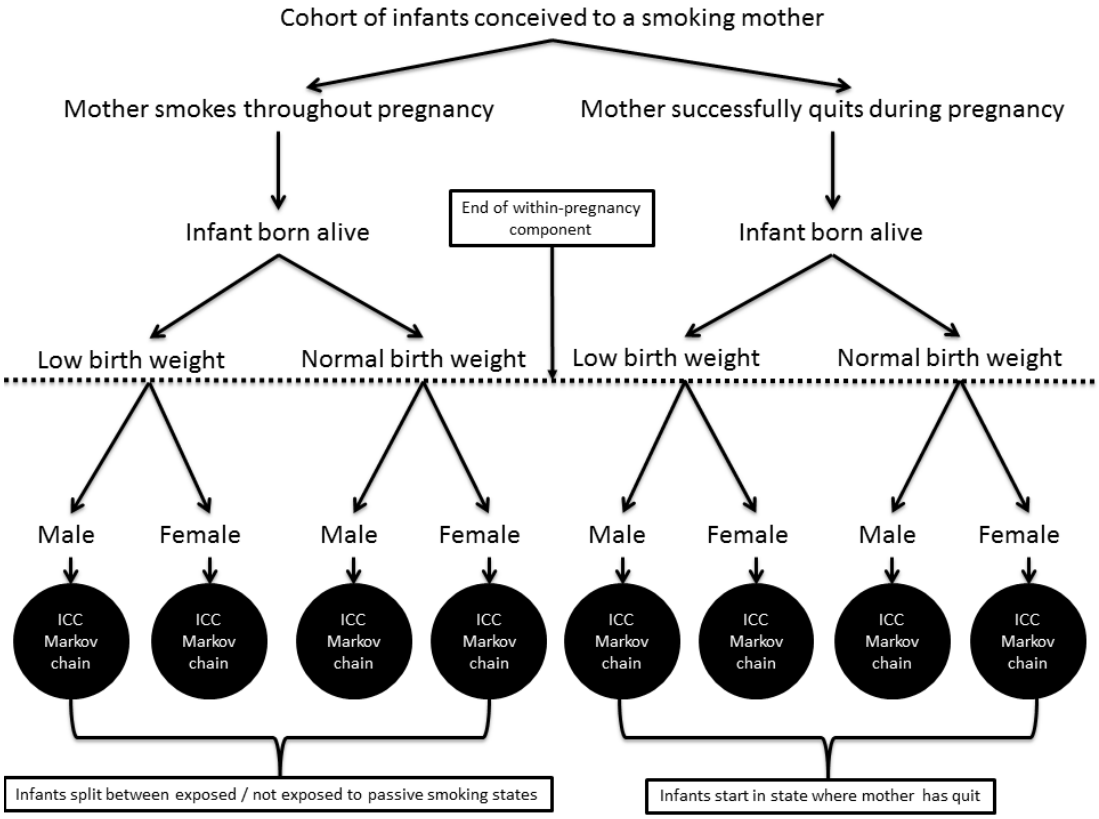
- Infants born to an abstinent mother with LBW
- Infants born to an abstinent mother with normal birth weight (NBW)
- Infants born to a smoking mother with LBW

- Infants born to a smoking mother with NBW
- Foetuses lost to an abstinent mother
- Foetuses lost to a smoking mother

Since the IWPC does not estimate the number of males and females, but the ICC requires this, the four virtual cohorts have to be split by gender (assumed to be 51% male). This generates eight virtual cohorts which then utilise eight corresponding Markov chains of the ICC, which are demonstrated in Figure 8.2.

Children who are born to an abstinent mother enter the ICC in the state which represents that the mother has quit, i.e. 'mother 0-1 year quitter infant not passive smoking', referred to as 'mother has quit' in Figure 8.1. The infants born to a smoking mother are split between the exposed and not-exposed passive smoking states as seen in Figure 8.1 In the actual ICC the states are: 'Mother smokes infant passive smoking' and 'mother smokes infant not passive smoking'. The proportion exposed to passive smoking is programmable by the user in ESIP, but is assumed to be 23% in the baseline analysis (see Section 7.4.4). A detailed representation of the ICC can be found in Chapter 7, Figure 7.2. The within-pregnancy healthcare costs associated with the infants are then attributed to the relevant ICC chains as sunk costs.

Figure 8.2: Infant cohort flow through the infant within-pregnancy component (IWPC) into the infant childhood component (ICC), demonstrating how the IWPC generates eight virtual cohorts



8.4 Construction of ESIP in Microsoft Excel

This section describes how ESIP was constructed in a software package for performing economic evaluations of cessation interventions. Initially, this focuses on the construction of the deterministic model; the probabilistic model will be discussed later. ESIP was constructed in Microsoft Excel 2010 [352]; Excel was chosen because it:

- contains many of the functions required to construct an economic model
- is an easy to use graphical interface, allowing straightforward interpretation and programming
- is widely available, allowing easy circulation of the finished version

The Excel spreadsheet consists of several 'worksheets' which contain the various information and parameters required for ESIP to work. ESIP requires programming using

the ‘program sheet’ worksheet to operate, which allows the user to select various options, including:

1. Cohort size
2. Base year
3. Average age of mother
4. Control and intervention group quit rates
5. Control and intervention group costs
6. Discount rates for costs and QALYs (initially set to 3.5% for costs and QALYs as per NICE guidance)[36]
7. Proportion of infants who are male (initially set to 51%)
8. Proportion of mothers who expose their child to passive smoking (initially set to 23%)
9. A reference age at which the user wishes the MLC model to estimate the outputs for (e.g. this could be set to average life expectancy for the mother, or simply to age 100)

8.4.1 Adapting ESIP for within-trial analyses

In Section 6.5.1, the general population relapse probabilities for up to two years postpartum were described for women who had quit during pregnancy. However, it was highlighted in Section 4.4.4 that there appeared to be a difference in postpartum relapse between control and intervention participants within trials, not only between the intervention and control groups, but also compared to the general population relapse. Therefore, as an added element of flexibility in ESIP, the user can select whether they wish to use specific relapse estimates for control and intervention participants. The probability of remaining abstinent was calculated using the same method as described in Section 6.5.1. The relevant abstinence proportions are presented in Table 8.1, while Table 8.2 gives the calculated probabilities.

Table 8.1: Proportion abstinent (95% confidence interval) amongst trial participants by control and intervention groups for up to two years postpartum

Years after pregnancy	Control group	Intervention group
End of pregnancy	0.093 (0.070 – 0.117)	0.146 (0.122 – 0.170)
1	0.060 (0.025 – 0.095)	0.085 (0.024 – 0.146)
2	0.043 (-0.030 - 0.116)	0.051 (-0.017 – 0.119)

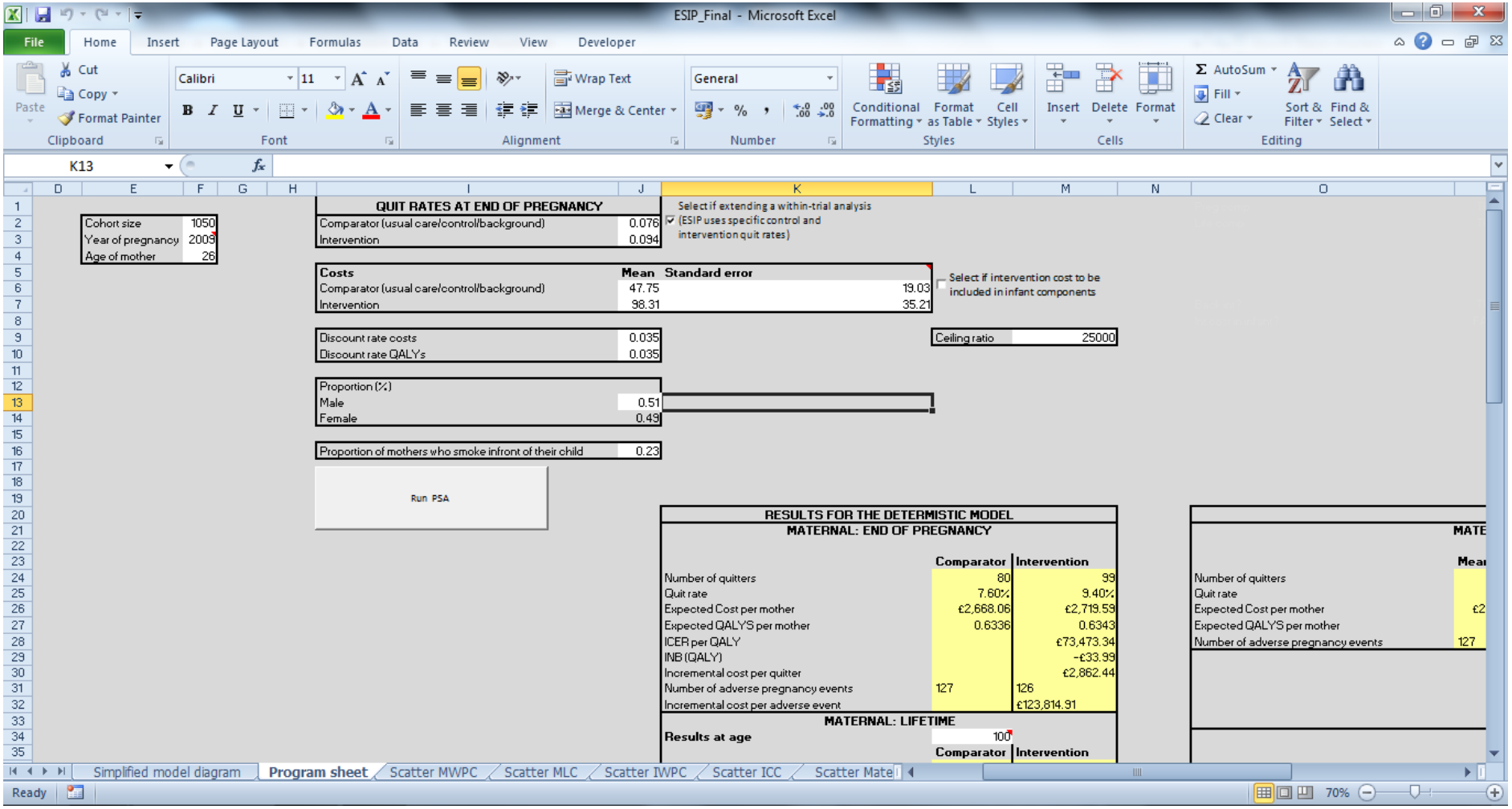
Table 8.2: Transition probabilities for up to two years postpartum by control and intervention groups

Transition probability	Control group	Intervention group
P(1-2 quit|0-1 quit)	0.6452	0.5822
P(Long-term quit|1-2 quit)	0.7167	0.6000

8.4.2 Modelling the impact of interventions

To enable the model to estimate the impact of different cessation interventions, the 'Program sheet' worksheet of the Excel file has two cells allowing the user to input the quit rates for two groups: the 'no intervention', or control group, and the intervention group. The comparator group rate represents the proportion who quit either without any intervention in a population study, or the quit rate of those found in the control group if the study is a clinical trial. The quit rate for the intervention group represents the proportion who quit if the smoking cessation intervention is utilised. There are a further four cells allowing the user to input the mean cost of the interventions and the interventions' cost standard error. This is shown in the screenshot in Figure 8.3.

Figure 8.3: Screenshot of the 'Program sheet' of ESIP, demonstrating the relevant cells for inputting appropriate quit rates and costs



The ESIP model itself consists of four worksheets which contain the combined maternal and infant components required. These are:

1. “Mother background”: Maternal components (MWPC and MLC) for the background/control/spontaneous quitting group of women who are smoking at conception
2. “Mother intervention”: Maternal components (MWPC and MLC) for the intervention group of women who are smoking at conception
3. “Infant background”: Infant components (IWPC and ICC) for the background/control/spontaneous quitting group of conceived infants
4. “Infant intervention”: Infant components (IWPC and ICC) for the intervention group of conceived infants

The quit rates and costs estimated for the background/control/spontaneous quitting group are fed into the worksheets with ‘background’ in their title, while rates and costs associated with the intervention group are used in the worksheets with ‘intervention’ in their title.

8.4.3 Output from the individual components

The ESIP model returns outputs from each component, which is summarised on the ’program sheet’ worksheet. This allows the user to look at the model estimates of various parameters for both the within-pregnancy, and the lifetime/childhood components for both mother and infant. For the maternal components, the following information is summarised from the output for both the control/background and intervention groups. The information reported for both maternal and infant components is summarised in Table 8.3.

Table 8.3: Estimated results computed by the ESIP model as summarised on the 'program sheet' in the Excel workbook

	Maternal components	Infant components
Within-pregnancy components	Number of quitters	Number of infants alive at birth
	Quit rate	Number of infants lost (ectopic, miscarried, stillborn)
	Expected cost per mother	Number of stillbirths
	Expected QALYs per mother	Number of premature births
	Number of maternal adverse pregnancy events	Number of infants with LBW
		Number of all infant adverse live births (LBW or premature or both)
		Number of all adverse infant outcomes (all adverse live births plus all infants lost)
		Expected cost per infant
Lifetime/childhood components	Percentage of cohort alive at reference age	Percentage of cohort alive at age 15 years
	Percentage of those alive at reference age with a co-morbidity	Percentage of cohort dead at age 15
	Expected cost per mother	Percentage of asthma amongst infants alive at age 15
	Expected life years per mother	Expected cost per child
	Expected QALYs per mother	Expected life years per child
		Expected QALYs per child

8.4.4 Outputs from the overall ESIP model

The results above can be used to calculate statistics to demonstrate the cost-effectiveness of any cessation intervention during pregnancy. As discussed in section 1.6.8, the most commonly used is the incremental cost-effectiveness ratio (ICER). ESIP calculates the following ICERs:

1. Incremental cost per quitter at the end of pregnancy for the mother
2. Incremental cost per QALY at the end of pregnancy for the mother
3. Incremental cost per quitter at reference age for the mother
4. Incremental cost per life year gained at reference age for the mother
5. Incremental cost per QALY at reference age for the mother
6. Incremental cost per premature or LBW or both avoided
7. Incremental cost per adverse pregnancy outcome for the infant (foetal loss, premature birth, LBW) at the end of pregnancy
8. Incremental cost per life year gained by the age of 15 for the child
9. Incremental cost per QALY for the child at age 15

ESIP also estimates the incremental net benefit statistic (INB). ESIP calculates the following INB statistics:

1. Incremental net benefit per QALY for the mother at the end of pregnancy
2. Incremental net benefit per life year gained for the mother at the reference age
3. Incremental net benefit per QALY for the mother at the reference age
4. Incremental net benefit per adverse live birth avoided (IWPC)
5. Incremental net benefit per adverse pregnancy outcome for the infant
6. Incremental net benefit per life year gained for the child at age 15
7. Incremental net benefit per QALY for the child at age 15

The calculation of the ICER and INB statistics allow ESIP to inform the user of the cost-effectiveness of the inputted interventions compared to its control group. Calculating the ICERs and INBs at the end of each component allows the user to determine the cost-effectiveness of the interventions either at the end of pregnancy or at a particular reference age after pregnancy. Furthermore, the way the Excel spreadsheet is set up allows the interventions to be compared at a trial-based as well as a population- based level, by

simply changing the parameters in the program sheet (e.g. cohort size) to either match the population in the trial or the population as a whole.

8.5 Making ESIP probabilistic

8.5.1 Adding uncertainty to the ESIP model

ESIP was adapted to conduct a probabilistic analysis by assigning statistical distributions to all parameters. The distributions described in Section 1.6.10 of this thesis were used for this, along with the various methods to fit the distributions to the parameters. Where no standard error for a particular parameter was identified, it was not excluded from the model, but a conservative estimate of 10% of the mean was assumed, as recommend by the CHEERS statement and other work. [43, 114-116] The utility decrements from Maheswaran et al were sampled once [295], and then used throughout the model, hence are only reported in the within-pregnancy part. For utility values regarding active smokers, the weighted average of the individual sampled decrement was calculated as described in Section 5.5. For cost associated with infants born with LBW and/or prematurely, the individual components were sampled and a weighted average value was calculated for inclusion in the model. The MLC parameters for abstinence one year after pregnancy and two years after pregnancy were calculated by sampling the proportions abstinent at the end of pregnancy, one year postpartum, and two years postpartum, then recalculating the associated probability before entering the MLC parameter alongside the Dirichlet estimated probabilities for Mother and Infant Mortality in the ICC. The PSA did not adjust the values for the fact they were self-reported outcomes. Table 8.4 gives the distributions assigned to the parameters in all components. The user should be aware that the parameterisation of the Dirichlet distribution related to mother and infant general population mortality (not adjusted for smoking behaviour) is not given. This is because the distribution is different for each year of age, and is also user selected when the user programmes in the base year of the evaluation and the age of the mothers in the cohort. This would mean that the author would need to report the parameterisation of approximately 10,000 Dirichlet distributions from the MLC and a further 1,500 distributions from the ICC. However, they were parameterised using the method described in section 1.6.10 where the probability of death (represented here as Ω) at the chosen age was

multiplied by 1,000, and fitted to the Dirichlet using the Gamma distribution as an approximation, so the parameterisation for each of the Dirichlet mortality values in the MLC and ICC would be $X \sim Gamma(1000 \times \Omega, 1)$. Although the standard error was not reported by the ONS estimates, the method of applying the Gamma distribution introduces a standard error, which can be calculated by $\sigma = \sqrt{\mu\beta}$. If the user wishes to view the estimated Dirichlet probabilities, these can be found in the ESIP spreadsheet under the worksheets entitled "Dirichlet probabilities" for estimates associated with the mother and "Dirichlet probs childhood" for estimates relating to the infant's childhood.

Table 8.4: List of parameters with associated distribution used in the PSA

Component	Parameter	Distribution	Mean	Standard Error	α	β
Within-pregnancy component (MWPC and IWPC)	P(Ectopic pregnancy)	Dirichlet	0.0151	0.0001**	74,926‡	1‡
	P(Miscarriage)	Dirichlet	0.0606	0.0001**	300,990‡	1‡
	P(Not abortive)	Dirichlet	0.9243	0.0001**	4,592,445‡	1‡
	P(Placental abruption)	Dirichlet	0.0037	0.00003**	17,101‡	1‡
	P(Placenta previa)	Dirichlet	0.0062	0.00004**	28,610‡	1‡
	P(Pre-eclampsia)	Dirichlet	0.0188	0.0001**	86,151‡	1‡
	P(No complication)	Dirichlet	0.9713	0.00007**	4,460,583‡	1‡
	P(Premature|abruption)	Beta	0.4029	0.0095**	1,074	1,592
	P(Premature|previa)	Beta	0.2631	0.0066**	1,163	3,257
	P(Premature|pre-eclampsia)	Beta	0.2739	0.0039**	3,618	9,593
	P(Premature|no complication)	Beta	0.0627	0.0003**	40,787	610,171
	P(LBW|premature)	Beta	0.6126	0.0014**	184,290	116,552
	P(LBW|full gestation)	Beta	0.0303	0.0001**	118,294	3,791,721
	P(Mother dies|ectopic)	Beta	0.00015	0.00004**	17	110,726
	P(Mother dies|miscarriage)	Beta	0.00002	0.000006**	7	444,864
	P(Mother dies|abruption)	Beta	0.00032	0.0001**	8	25,268
	P(Mother dies|previa)	Beta	0.00002	0.00002**	1	42,285

	P(Mother dies|pre-eclampsia)	Beta	0.00025	0.00004**	32	127,302
	P(Mother dies|no complication)	Beta	0.00006	0.000003**	382	6,592,480
	P(Infant stillborn|LBW|premature)	Beta	0.0680	0.0006**	12,530	17,160
	P(Infant stillborn|NBW|premature)	Beta	0.0071	0.0002**	828	115,724
	P(Infant stillborn|LBW|full gestation)	Beta	0.0177	0.0004**	2,095	116,199
	P(Infant stillborn|NBW|full gestation)	Beta	0.0017	0.00002**	6,577	3,785,144
	OR(Ectopic)	Log normal	1.77	0.2321	0.5710†	0.1346†
	OR(Miscarriage)	Log normal	1.32	0.0765	0.2776†	0.0578†
	OR(Placental abruption)	Log normal	1.62	0.0791	0.4824†	0.0491†
	OR(Placenta previa)	Log normal	1.58	0.2755	0.4574†	0.1817†
	OR(Pre-eclampsia)	Log normal	0.51	0.0663	-0.6733†	0.1330†
	OR(Premature birth)	Log normal	1.27	0.0306	0.2390†	0.0946†
	RR(LBW)	Log normal	1.82	0.0765	0.5988†	0.1652†
	RR(Stillbirth)	Log normal	1.26	0.0383	0.2311†	0.1187†
	Cost(Ectopic pregnancy)	Gamma	£1,749.23	£674.39	6.72779	260.001
	Cost(Miscarriage)	Gamma	£554.70	£236.94	5.48092	101.206
	Cost(Midwife visit)	Gamma	£53.00	£18.18	8.49685	6.23761
	Cost(Standard ultrasound scan)	Gamma	£109.78	£53.08	4.27769	25.6634

	Cost(Specialised ultrasound scan)	Gamma	£121.02	£66.94	3.2683	37.0284
	Cost(Obstetrician first visit)	Gamma	£152.21	£57.95	7.2463	13.9561
	Cost(Obstetrician subsequent visit)	Gamma	£101.13	£37.75	7.2463	13.9561
	Cost(Normal birth)	Gamma	£2,079.81	£633.14	10.7905	192.744
	Cost(Emergency caesarean)	Gamma	£3,466.59	£872.97	15.7692	219.833
	Cost(Caesarean birth)	Gamma	£3,413.47	£873.91	15.2566	223.737
	Cost(Routine observation)	Gamma	£571.15	£310.59	3.38171	168.894
	Cost(Death)	Gamma	£1,379.02	£615.42	5.021	274.65
	Cost(Hypertension drugs (premature))	Gamma	£53.05	£5.31*	100	0.5305
	Cost(Hypertension drugs (full gestation))	Gamma	£63.66	£6.37*	100	0.6366
	Cost(Infant stillborn)	Gamma	£722.65	£72.27*	100	7.2265
	Cost(Premature 20-23 weeks gestaion)	Gamma	£1,261.00	£2,790.00	0.20	6,172.96
	Cost(Premature 24-27 weeks gestation)	Gamma	£7,362.00	£9,692.00	0.58	12,759.42
	Cost(Premature 28-31 weeks gestation)	Gamma	£6,920.00	£4,909.00	1.99	3,482.41
	Cost(Premature 32-36 weeks gestation)	Gamma	£1,917.00	£1,586.00	1.46	1,312.15

	Cost(Full gestation)	Gamma	£824.00	£940.00	0.77	1,072.33
	Cost(Birth weight <1000g)	Gamma	£6,430.00	£9,642.00	0.44	2,715.08
	Cost(Birth weight 1000-1499g)	Gamma	£5,779.00	£5,310.00	1.18	23,227.45
	Cost(Birth weight 1500-1999g)	Gamma	£3,234.00	£3,119.00	1.08	3,191.13
	Cost(Birth weight 2000-2499g)	Gamma	£1,606.00	£1,256.00	1.63	3,359.02
	Cost(NBW)	Gamma	£835.00	£978.00	0.73	519.16
	Utility(Constant)	Beta	0.987	0.0066	286.89	3.7787
	Utility(Active light smoker decrement)	Beta	0.044	0.0069	38.9689	846.6872
	Utility(Active moderate smoker decrement)	Beta	0.055	0.0069	60.2012	1,034.36662
	Utility(Active heavy smoker decrement)	Beta	0.087	0.0102	66.2814	695.5739
	Utility(Former smoker decrement)	Beta	0.027	0.0043	37.6880	1,358.1656
	Utility(Female decrement)	Beta	0.016	0.0036	19.7333	1,213.5963
	Utility(Age 25-34 decrement)	Beta	0.015	0.0054	7.7074	506.1193
	Utility(Age 35-44 decrement)	Beta	0.033	0.0056	33.4004	978.7342
	Utility(Age 45-54 decrement)	Beta	0.068	0.0061	114.9017	1,574.8291
	Utility(Age 55-64 decrement)	Beta	0.094	0.0066	181.8800	1,753.0136
	Utility(Age 65-74 decrement)	Beta	0.116	0.0077	202.9784	1,546.8351

	Utility(Age 75+ decrement)	Beta	0.138	0.0084	231.4999	1,446.0359
	Utility(Ectopic pregnancy decrement)	Beta	0.01	0.01	0.98	97.02
	Utility(Loss of infant decrement)	Beta	0.1	0.1	0.8	7.2
Mother Lifetime Component (MLC)	Proportion (abstinent at end of pregnancy)	Beta	0.126	0.0099	140.0570	971.5067
	Proportion (abstinent at one year postpartum)	Beta	0.074	0.0242	8.5597	107.1125
	Proportion (abstinent at two year postpartum)	Beta	0.047	0.0360	1.5801	32.0397
	P(Quit attempt during first year postpartum given smoked throughout pregnancy)	Dirichlet	0.13	0.0106**	130‡	1‡
	P(Abstinent at one year postpartum having quit during pregnancy)	Dirichlet	Dependent on sampled values from Proportion(abstinent at one year postpartum) divided by Proportion (abstinent at end of pregnancy)			
	P(Abstinent at two years postpartum having quit during pregnancy)	Dirichlet	Dependent on sampled values from Proportion(abstinent at two years postpartum) divided by Proportion (abstinent at one year postpartum)			
	P(Quit attempt during any year given current smoker)	Dirichlet	0.27	0.0140**	270‡	1‡

	P(Abstinent at one year after quit attempt)	Dirichlet	0.14	0.0110**	140‡	1‡
	P(Abstinent at two years after quit attempt)	Dirichlet	0.57	0.0156**	570‡	1‡
	P(Relapse given long-term quitter)	Dirichlet	0.0086	0.0029**	8.6262‡	1
	RR(CHD|Smoker aged 35-54)	Log normal	4.98	0.498*	1.6054†	0.1013†
	RR(CHD|Smoker aged 55-64)	Log normal	3.25	0.325*	1.1787†	0.1013†
	RR(CHD|Smoker aged 65-74)	Log normal	3.29	0.329*	1.1909†	0.1013†
	RR(CHD|Smoker aged 75+)	Log normal	2.25	0.225*	0.8109†	0.1013†
	RR(CHD|Former smoker aged 35-54)	Log normal	2.23	0.223*	0.8020†	0.1013†
	RR(CHD|Former smoker aged 55-64)	Log normal	1.21	0.121*	0.1906†	0.1013†
	RR(CHD|Former smoker aged 65-74)	Log normal	1.56	0.156*	0.4447†	0.1013†
	RR(CHD|Former smoker aged 75+)	Log normal	1.42	0.142*	0.3507†	0.1013†
	RR(COPD|Smoker aged 35-54)	Log normal	6.43	0.643*	1.8610†	0.1013†
	RR(COPD|Smoker aged 55-64)	Log normal	9.00	0.9*	2.1972†	0.1013†
	RR(COPD|Smoker aged 65-74)	Log normal	38.89	3.889*	3.6607†	0.1013†

	RR(COPD|Smoker aged 75+)	Log normal	20.96	2.096*	3.0426†	0.1013†
	RR(COPD|Former smoker aged 35-54)	Log normal	1.85	0.185*	0.6152†	0.1013†
	RR(COPD|Former smoker aged 55-64)	Log normal	4.84	0.484*	1.5769†	0.1013†
	RR(COPD|Former smoker aged 65-74)	Log normal	15.72	1.572*	2.7549†	0.1013†
	RR(COPD|Former smoker aged 75+)	Log normal	7.06	0.706*	1.9544†	0.1013†
	RR(LC|Smoker aged 35-54)	Log normal	13.30	1.33*	2.5878†	0.1013†
	RR(LC|Smoker aged 55-64)	Log normal	18.95	1.895*	2.9418†	0.1013†
	RR(LC|Smoker aged 65-74)	Log normal	23.65	2.365*	3.1634†	0.1013†
	RR(LC|Smoker aged 75+)	Log normal	23.08	2.308*	3.1390†	0.1013†
	RR(LC|Former smoker aged 35-54)	Log normal	2.64	0.264*	0.9708†	0.1013†
	RR(LC|Former smoker aged 55-64)	Log normal	5.00	0.5*	1.6094†	0.1013†
	RR(LC|Former smoker aged 65-74)	Log normal	6.80	0.680*	1.9169†	0.1013†
	RR(LC|Former smoker aged 75+)	Log normal	6.38	0.638*	1.8532†	0.1013†

	RR(Stroke|Smoker aged 35-54)	Log normal	2.44	0.244*	0.8920†	0.1013†
	RR(Stroke|Smoker aged 55-64)	Log normal	1.98	0.198*	0.6831†	0.1013†
	RR(Stroke|Smoker aged 65-74)	Log normal	2.27	0.227*	0.8198†	0.1013†
	RR(Stroke|Smoker aged 75+)	Log normal	1.70	0.170*	0.5306†	0.1013†
	RR(Stroke|Former smoker aged 35-54)	Log normal	1.00	0.1*	0.0000†	0.1013†
	RR(Stroke|Former smoker aged 55-64)	Log normal	1.10	0.11*	0.0953†	0.1013†
	RR(Stroke|Former smoker aged 65-74)	Log normal	1.24	0.124*	0.2151†	0.1013†
	RR(Stroke|Former smoker aged 75+)	Log normal	1.10	0.11*	0.0953†	0.1013†
	RR(Death|Current smoker aged 35-44)	Log normal	1.75	0.175*	0.5596†	0.1013†
	RR(Death|Current smoker aged 45-54)	Log normal	2.025	0.2025*	0.7056†	0.1013†
	RR(Death|Current smoker aged 55-64)	Log normal	2.1368	0.21368*	0.7593†	0.1013†
	RR(Death|Current smoker aged 65-74)	Log normal	1.9831	0.19831*	0.6847†	0.1013†
	RR(Death|Current smoker aged	Log normal	1.5727	0.1527*	0.4528†	0.1013†

	75-84)					
	RR(Death|Current smoker aged 85+)	Log normal	1.2972	0.12972*	0.2602†	0.1013†
	RR(Death|Former smoker aged 35-44)	Log normal	1.25	0.125*	0.2231†	0.1013†
	RR(Death|Former smoker aged 45-54)	Log normal	1.2250	0.12250*	0.2029†	0.1013†
	RR(Death|Former smoker aged 55-64)	Log normal	1.4105	0.14105*	0.3440†	0.1013†
	RR(Death|Former smoker aged 65-74)	Log normal	1.3333	0.13333*	0.2877†	0.1013†
	RR(Death|Former smoker aged 75-84)	Log normal	1.1469	0.11469*	0.1370†	0.1013†
	RR(Death|Former smoker aged 85+)	Log normal	1.0658	0.10658*	0.0638†	0.1013†
	Cost(CHD)	Gamma	£3,954.46	£395.46*	100	39.55
	Cost(COPD)	Gamma	£1,121.00	£112.10*	100	11.21
	Cost(Lung Cancer)	Gamma	£9,075.81	£907.58*	100	90.76
	Cost(Stroke)	Gamma	£1,627.76	£162.78*	100	16.28
	Cost(Death)	Gamma	£1,379.02	£615.42	5.021	274.65
	Utility(CHD)	Beta	0.73	0.3	2.7079	1.0016

	Utility(COPD)	Beta	0.73	0.23	1.9899	0.7360
	Utility(Lung cancer)	Beta	0.67	0.22	2.3907	1.1775
	Utility(Stroke)	Beta	0.72	0.32	0.6975	0.2713
Infant Childhood component (ICC)	P(Mother exposes her child to smoking)	Beta	0.23	0.0419**	23	77
	P(Mother makes quit attempt during first year postpartum given smoked throughout pregnancy)	Dirichlet	0.13	0.0106**	130‡	1‡
	P(Mother abstinent at one year postpartum having quit during pregnancy)	Dirichlet	Dependent on sampled values from Proportion(abstinent at one year postpartum) divided by Proportion (abstinent at end of pregnancy)			
	P(Mother abstinent at two years postpartum having quit during pregnancy)	Dirichlet	Dependent on sampled values from Proportion(abstinent at two years postpartum) divided by Proportion (abstinent at one year postpartum)			
	P(Mother makes quit attempt during any year given current smoker)	Dirichlet	0.27	0.0140**	270‡	1‡
	P(Mother abstinent at one year after quit attempt)	Dirichlet	0.14	0.0110**	140‡	1‡
	P(Mother abstinent at two years after quit attempt)	Dirichlet	0.57	0.0156**	570‡	1‡

P(Mother relapses given long-term quitter)	Dirichlet	0.0086	0.0029**	8.6262‡	1
OR(Death|LBW, aged 1-4)	Log normal	2.2	0.1531	0.7885†	0.2744†
OR(Death|LBW, aged 5-9)	Log normal	1.7	0.2041	0.5306†	0.4796†
OR(Death|LBW, aged 10-14)	Log normal	1.5	0.2041	0.4055†	0.5465†
OR(Death|LBW, aged 15-19)	Log normal	0.9	0.1020	-0.1054†	0.4520†
OR(Asthma due to being born with LBW)	Log normal	1.28	0.1046	0.2469†	0.3193†
OR(Asthma due to exposure during pregnancy, aged 0-2 years)	Log normal	1.85	0.3010	0.6152†	0.6281†
OR(Asthma due to exposure during pregnancy, aged 3-4 years)	Log normal	1.30	0.2653	0.2624†	0.7802†
OR(Asthma due to exposure during pregnancy, aged 5-18 years)	Log normal	1.23	0.0612	0.1823†	0.1942†
OR(Asthma due to exposure to passive smoking during childhood, aged 0-2 years)	Log normal	2.47	2.2296	0.9042†	2.6704†
OR(Asthma due to exposure to passive smoking during childhood, aged 3-4 years)	Log normal	1.05	0.0944	0.0488†	0.3510†

	OR(Asthma due to exposure to passive smoking during childhood, aged 5-18 years)	Log normal	1.20	0.1173	0.1823†	0.3848†
	Cost(asthma)	Gamma	£428.51	£510.39	0.7049	607.9157
	Cost(Death)	Gamma	£1,379.02	£615.42	5.021	274.65
	Utility(Child with asthma)	Beta	0.9	0.18	1.6	0.1778
Relapse values associated with within-trial analyses (see section 8.4.1)	Proportion(abstinent at end of pregnancy controls)	Beta	0.093	0.0120	54.4765	531.2919
	Proportion (abstinent at one year postpartum controls)	Beta	0.06	0.0179	10.5522	165.3182
	Proportion (abstinent at two years postpartum controls)	Beta	0.043	0.0372	1.236	27.4326
	Proportion(abstinent at end of pregnancy interventions)	Beta	0.146	0.0122	121.2637	709.3094
	Proportion (abstinent at one year postpartum interventions)	Beta	0.085	0.0311	6.7401	72.5556
	Proportion (abstinent at two years postpartum interventions)	Beta	0.051	0.0347	1.9997	37.2100
Overall ESIP model	P(Quit rate at end of pregnancy for comparator)	Beta	User specified	User specified	N/A	N/A

	P(Quit rate at end of pregnancy in intervention)	Beta	User specified	User specified	N/A	N/A
	Cost(Comparator)	Gamma	User specified	User specified	N/A	N/A
	Cost(Intervention)	Gamma	User specified	User specified	N/A	N/A

***=** These are assumed standard errors, based on 10% of mean value

****=** The standard errors are not reported in the literature estimates, however they are approximated by backtracking the fitting of the distribution to give an estimate of the standard error that the parametrisation of the distribution assigns

†= These represent the natural log of the mean and its associated standard error for parameterising the log normal distribution, with values in the α representing the mean of the log normal distribution, and values in the β representing the standard error of the log normal distribution

‡= These represent the values programmed into the Gamma distribution in Excel as a proxy to the Dirichlet distribution

8.5.2 Conducting the PSA in ESIP

The PSA, as programmed in ESIP, randomly samples each parameter as specified above, and evaluates the model. Because of the large number of parameters with distributions fitted, there is likely to be a high degree of uncertainty in ESIP. As discussed in section 1.6.10, it was decided that the PSA would require 10,000 iterations to achieve stability and to produce reasonable estimates as the CIs associated with the output. The PSA can be activated from the 'Program sheet' worksheet in the Excel file, as ESIP can be run in both deterministic and probabilistic modes.

8.5.3 Output from the PSA in ESIP

The 'Simulation' worksheet in the Excel file records the parameters' chosen values in each PSA iteration as well as the output generated by the model. This allows basic summary statistics such as mean and 95% CI for both the parameters and model outputs to be generated.

Further output from the PSA includes a scatterplot of incremental costs against incremental outcome. The scatterplots allow the user to visually inspect the orientation of the PSA estimates on the cost-effectiveness plane. Scatterplots are available for both the combined output for mother and infant as well as the three individual ESIP components which have incorporated QALYs as their incremental outcome; MWPC, MLC and ICC. In addition, a scatterplot using incremental adverse pregnancy events for the infant avoided is generated for the IWPC.

The ESIP model also calculates the cost-effectiveness acceptability curves (CEACs) which are used to represent uncertainty (see section 1.6.11). A CEAC plots the probability that an intervention (compared to the comparator) is cost-effective at a willingness to pay level chosen by a decision maker. [118, 353] The ESIP model generates CEACs for each ESIP component and the merged output for mother and infant, estimating the probability the intervention is cost-effective in terms of QALYs, life years gained (LYG), number of quitters,

and adverse pregnancy events/birth outcomes for the mother/infant. The willingness to pay can be chosen from between £0 to £100,000 per outcome, and CEACs are automatically generated by the PSA.

8.6 Discussion

This chapter has described the combination of the four standalone components to create ESIP. ESIP estimates the potential impacts of smoking and cessation in pregnancy not only on the health of the mother, but on the infant as well, and assesses any lasting impact on the health of both beyond pregnancy. Furthermore, ESIP allows comparisons between interventions, enabling it to estimate the cost-effectiveness of cessation interventions during pregnancy. This section aims to critically appraise ESIP, and suggest further refinements and future research.

8.6.1 The ESIP model in context of the literature

Although there are several studies that have addressed the topic of smoking and smoking cessation during pregnancy, there are relatively few economic models that have investigated the fiscal impacts of smoking/smoking cessation during pregnancy, most being within-trial evaluations. As Chapter 3 identified, most models focused on the within-pregnancy impacts of smoking on the health and healthcare costs for the mother or infant [65, 68, 205], with only two studies looking at both the mother and the infant [65], one only included two separate, unlinked models, while the other incorporated the prevalence of maternal complications and adverse birth outcomes. Two studies were identified as modelling the long-term impact of smoking during pregnancy on the health/costs of the mother and her infant for the rest of their lives.

One advantage of ESIP over the previous literature is that it combines four components to give a comprehensive visualisation of the natural flow of a cohort member from conception, through birth, and into the post-pregnancy period. Only four studies have been identified as exploring longer term impacts of smoking, with only two investigating long-

term impacts on both the mother and her child,[139, 190], and the others only including long-term maternal outcomes. [137, 196] ESIP is novel in that it simultaneously examines the within-pregnancy time horizon and post-pregnancy impacts. This allows ESIP to estimate both the within-pregnancy (short term) cost-effectiveness of cessation interventions and the longer term cost-effectiveness for both mother and infant. For decision makers, this could be particularly useful, since ESIP generates the necessary information which may suit their different perspectives, e.g. a decision maker may be more interested in the short-term cost-effectiveness for the mother than in the longer term impacts for the infant.

ESIP also has the advantage of being the first model in this topic area to incorporate the influence of the mother's smoking behaviour on the health and healthcare costs of her infant, both within-pregnancy and throughout the childhood period. While Shipp et al constructed two separate models to estimate the impact of smoking on pregnancy outcomes for both the mother and infant [65], there was no direct link between the two, so the mother's within-pregnancy smoking behaviour did not impact on the infant's health status at birth. ESIP incorporates this link, allowing the smoking behaviour within pregnancy to directly influence the pregnancy outcomes for the infant. The potential benefit of this link is that it is more representative of the impact of smoking within-pregnancy, implying that ESIP may produce better estimates of the cost-effectiveness of cessation interventions undertaken during pregnancy. Furthermore, ESIP includes a link between the mother's smoking behaviour post-pregnancy and the infant's exposure to passive smoking. Not only has this link not been incorporated before, but the information used to derive the parameters is potentially the most up-to-date estimates of smoking behaviour post-pregnancy.

Another advantage of ESIP is that it includes a PSA. Only two previous studies attempted a PSA, whereas the rest of the literature performed the analysis deterministically. The PSA undertaken by Mallender et al only captures uncertainty associated with the quit rates and costs of the interventions, and not that associated with other incorporated model parameters. [190] Tappin et al included a PSA with distributions fitted to all parameters where there was information regarding the uncertainty associated with the parameter,

including the long-term costs of smoking-related diseases, intervention quit and immediate postpartum relapse rates, and HRQoL weights. [196] This broad PSA approach has also been adopted by ESIP, which illustrates the impact of uncertainty associated with the parameters and demonstrates how important it is to incorporate all of these, rather than the selective approach adopted by Mallender at al. Other previous literature primarily used one- or two-way sensitivity analyses, which may not comprehensively capture the effects of uncertainty in all parameters [109], potentially resulting in misleading information and an incorrect decision. A PSA helps to mitigate the likelihood of this error occurring, since it includes an assessment of the likelihood that any decision made as a consequence of ESIP output is correct. This information is potentially more useful to decision makers compared to that generated from previous models' sensitivity analyses.

8.6.2 Limitations of the ESIP model

One consideration is that in the PSA, ESIP potentially breaks the 'influence link' between the mother and the child after pregnancy (the MLC and ICC). In the deterministic analysis, ESIP shares the MLC parameters with the ICC, allowing the mother's smoking behaviour to directly influence the health of her offspring. In the PSA, the parameters are no longer shared because the mother's smoking behaviour parameters in the ICC require a different distribution to the corresponding parameters in the MLC. This occurs because the MLC has a Dirichlet distribution with three categories, whereas the ICC has four categories, due to the addition of the risk of infant's mortality. Unlike the deterministic ICC, it is likely that during the PSA, the sampled parameter in the ICC is different to the corresponding parameter sampled in the MLC. The implication of this is that during the PSA, the link between the ICC and MLC is broken to some extent. The effect this has on the relationship between the two components is unclear and therefore the associated impact on the cost-effectiveness estimates and output of ESIP is also undetermined.

To try and mitigate the impact of this problem, the way the Dirichlet distribution is calculated in the ICC is such that in principle, the probabilities relating to the maternal smoking behaviour from the MLC are conservatively estimated. This would imply that the ICC will always slightly underestimate the changes in smoking behaviour compared to the

MLC. This effect is likely to be minimal and therefore the author does not anticipate any significant impact on the estimates of health and healthcare costs associated in the ICC. However, the user should be aware of this and consider whether this has a substantial impact on the output from ESIP.

Another limitation is that any self-reported values were not adjusted in the PSA. This is particular relevant to the one year and two year postpartum estimates from Chapter 4 of this thesis. Because these values were self-reported, it is possible that the values used in the PSA are too high, since it is possible that individuals reported abstinence when they were in fact smoking. However, as discussed in Chapter 4, there was no evidence of significant self-reporting bias between the biochemically validated abstinence and the self-reported abstinence, which suggests that using the self-reported data is not an issue. Furthermore, had solely biochemically validated data been used, there would not have been any data at one year and two year postpartum, since this data is self-reported only. Additionally, rather than put the distribution on the probability, the author put the distribution on the estimates of the proportion abstinent as generated by the meta-analysis, and allowed the model to recalculate the values based upon these estimates. This allows the probability to vary essentially between zero and one, reflecting the large uncertainty there is in the meta-analysis estimates, as well as controlling for any impact of self-reported data. This may introduce a greater amount of parameter, and hence decision, uncertainty into ESIP when compared to placing the distribution individually on the probability itself, but the author can only speculate as to how much this may be an issue, and warrant further investigation.

8.6.3 The impact of the assumptions on the output of the model

As discussed at the start of this chapter, ESIP makes five assumptions regarding the cohort of women and infants being modelled. Two of these assumptions are necessary for ESIP to function, such as that all infants are or were associated with a smoking mother, and that all women were current smokers at conception. It may be possible to relax the last assumption around the women smoking; however it would not seem logical that a cessation intervention would be given to those women who have already stopped smoking

at conception. These women are likely to be exposed to a relapse intervention, which is a different research question which would require a separate evaluation.

The other assumption relating to the mother is that there is no lasting impact of included pregnancy complications on maternal health, based upon the information generated in Chapter 2. With its current structure, ESIP could not incorporate the lasting impact of a complication, however, should future research identify that lasting impacts exist, then one modification to ESIP could be to increase the number of maternal cohort chains such that any later impact could be incorporated.

The assumption that all infant conceptions are singleton has been discussed in more detail in Chapter 7. This could be changed to either assuming that all conceptions are multiple (i.e. doubling or tripling the infant cohort size in relation to the mother cohort), or by increasing the infant cohort size by an appropriate figure representing the number of births in relation to the number of mothers (e.g. In 2012, it was estimated that the number of births (both liveborn and stillborn) in England and Wales was 733,232, while the number of maternities (number of women giving birth) was 721,574 [354], which suggests that the infant cohort should be 1.02 times greater than the cohort of mothers). It is unlikely that incorporating multiple pregnancies would make much difference to the outcomes from ESIP. Furthermore, it could be argued that, should interventions prove cost-effective for singleton births, then it is very likely that they are more so for multiple births. Therefore, the most conservative estimates for cost-effectiveness come from looking at singleton births and investigation into the cost-effectiveness of multiple births is not required.

The final assumption is that gender does not have any impact on the chance of an adverse birth outcome for the infant. This means that gender is not important in the IWPC, and that both males and females have the same chance of being born prematurely, with LBW, and stillborn. However, there is some evidence which suggests that these birth outcomes are contingent on gender, with males more likely to deliver prematurely or stillborn [355, 356], while females appear to be at a greater risk of LBW. [357] This suggests that gender is an important consideration in the IWPC, and therefore the IWPC should split the cohort of infants into males and females. However, it is unlikely that the inclusion of gender will

affect the overall estimates of adverse birth outcomes for the cohort, and unless there is a difference in healthcare costs for males and females, gender is unlikely to change the overall estimates of the cost-effectiveness at the end of pregnancy. However, the impact of gender might be important to incorporate into the ICC, since LBW is an important morbidity included in the model. Not including the impact of gender on birth outcomes for the infant would suggest that the ICC might be using inaccurate estimates of males and females, which could impact on the cost-effectiveness estimates generated by ESIP, although it is unclear what impact this may be.

8.7 Summary

This chapter has described how ESIP combines the four components to produce a comprehensive and novel economic model of the impacts of smoking during pregnancy. One advantage of ESIP compared to the previous literature is that it now includes a direct link between the mother's smoking behaviour both within-pregnancy and afterwards on the health of the infant. ESIP also incorporates a PSA, implying greater relevance to the modern decision making process. However, when undertaking the PSA, ESIP breaks that link as it needs to resample the parameters in the ICC and MLC. How much this is an issue to the analysis is unclear. Despite this consideration, ESIP gives the user and policy makers a far more comprehensive picture of the impacts on health and healthcare costs associated with smoking during pregnancy compared to the previous literature. In conclusion, the author suggests that ESIP is an improvement and is likely to produce more accurate cost-effectiveness estimates than any previous economic model. The following two chapters demonstrate the validity of the within-pregnancy components and the overall ESIP model, as well as demonstrating how ESIP can be used to perform an evaluation of within-pregnancy cessation interventions.

Chapter 9: Validity of the MWPC and IWPC

9.1 Introduction

The within-pregnancy components (MWPC and IWPC) of ESIP are based upon readily available population data. Therefore, it is possible to investigate whether ESIP can reproduce the population estimates of the within-pregnancy complications and birth outcomes. If ESIP can reproduce reasonably accurate measures of the number of complications/ birth outcomes, it would seem appropriate to assume that ESIP is producing accurate estimates of the costs and benefits of smoking and cessation during pregnancy. This section describes a validation exercise to determine whether this is the case. We compared the output of a PSA of the MWPC and IWPC with bootstrapped population estimates to see how close the output from the MWPC and IWPC were to population estimates. The user should note that the parameterisation of the PSA in ESIP is given in section 8.5 of this thesis.

9.2 Objective

To determine whether the MWPC and IWPC produce reasonable estimates of the number of occurrences of within-pregnancy complications for the mother and birth outcomes for the infant under a PSA.

9.3 Methods

9.3.1 Method of estimating the population mean distribution of maternal complications

To determine the distribution associated with the population mean estimates of the included conditions, non-parametric bootstrapping with replacement was utilised. [40] As discussed in section 1.6.10 of this thesis, to control for uncertainty and allow reasonably accurate 95% CI estimation, we performed 10,000 non-parametric bootstrap iterations of the HES data reported in Table 5.1 and Table 5.2. This was conducted using Stata v11.2. [239] Bootstrapped estimates were generated for the number of:

- Conceptions
- Ectopic pregnancies
- Miscarriages
- Placental abruption occurrences
- Placenta previa occurrences
- Pre-eclampsia occurrences

The bootstrapped mean number of conceptions for the population was used as the cohort size for ESIP. The quit rate was set to 88% as estimated from the latest IFS. [135] ESIP then performed a PSA (see Chapter 8), and the results of the two analyses were compared. Kernel density plots were created for each complication for both population bootstrapped estimates and model predictions.

9.3.2 Method of estimating the population mean distribution of maternal deaths

The above approach was adopted for estimating the number of maternal deaths. ONS data as reported in Table 5.8 was bootstrapped 10,000 times, as recommended as per section 1.6.10, giving an estimated mean number of maternities and maternal deaths. ESIP was then programmed with the cohort size set at the mean bootstrapped number of maternities, and a quit rate of 88%.

9.3.3 Method of estimating the population mean distribution of infant birth outcomes

Data for LBW and stillbirth was taken from ONS records. [283] For premature birth, the data used in Table 5.10 was utilised. In the ONS dataset for Gestation Specific Infant Mortality, the years 2007 and 2008 were merged. [286] Because no other data was available, the values for premature births were split equally between the two years. The data used for the non-parametric bootstrapping is given in Table 9.1.

Table 9.1: Estimates of infant birth outcomes as used to inform the non-parametric bootstrapping

Year	Live births	Stillbirths	LBW (Live births + stillbirths)	Premature births (live births + stillbirths)
2003	621,469*	3,585*	49,987*	*No data*
2004	639,721*	3,689*	50,697*	*No data*
2005	645,835*	3,483*	50,657*	*No data*
2006	669,601*	3,602*	52,544*	52,581‡
2007	690,013*	3,598*	51,648*	51,877.5‡
2008	708,711†	3,617†	52,820†	51,877.5‡
2009	706,248†	3,688†	52,819†	52,648‡
2010	723,165†	3,714†	52,701†	52,223‡
2011	723,913†	3,811†	53,293†	52,993‡
2012	729,674†	3,558†	53,268†	*No data*
*= Source: Table 8, Child Mortality Statistics for England and Wales 2003-2007 **[293, 294, 358-360]**				
†= Source: Table 6, Child Mortality Statistics for England and Wales 2008-2012 **[289-292, 361]**				
‡= Source: Table 5.10, Chapter 5.				

Mean and CIs for the number of live births and birth outcomes were generated using non-parametric bootstrapping with 10,000 iterations, as recommended in section 1.6.10. The cohort size was determined by the number of live births plus stillbirths. For this exercise, ESIP was programmed such that there were no pregnancies that did not end in delivery (i.e. no ectopic pregnancy and miscarriage). The quit rate in ESIP was set to 88%, and ESIP performed a PSA with 10,000 iterations, to allow accurate 95% CI estimation, as recommended in section 1.6.10. The results of the two analyses were then compared.

9.4 **Results**

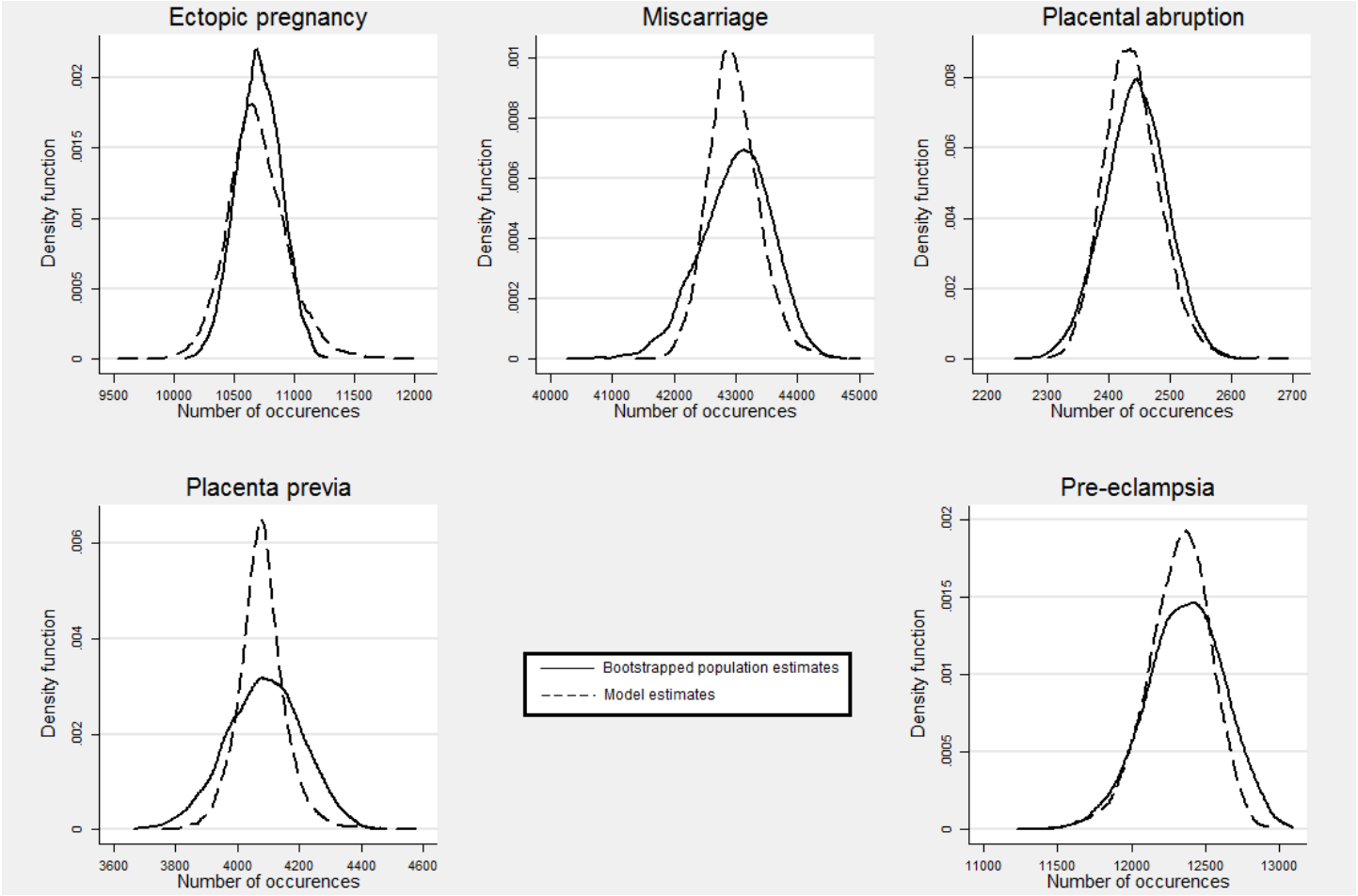
9.4.1 Maternal complications

Table 9.2 reports the results of the two analyses. The final column shows the differences between the two means (bootstrapped population mean – predicted ESIP mean). The cohort size for the PSA was 709,736 conceptions. For all complications, ESIP's mean estimated number of occurrences was below the bootstrapped population means, and the CIs did not cross. Figure 9.1 demonstrates the Kernel density plots for the bootstrapped population means and model estimates. Visual inspection suggested that ESIP produced a similar shaped distribution for all maternal complications, with both distributions for the population mean and ESIP output crossing for all complications. Differences in the means appeared to be relatively small. There appeared to be a greater degree of uncertainty in the ESIP estimates for ectopic pregnancy as this was the only complication where the predicted ESIP CI was wider than the population estimate.

Table 9.2: Results of the non-parametric bootstrapping for HES NHS Maternity statistics for England compared to the ESIP model predicted output

	Bootstrapped population estimates			**Model PSA estimates**			**Difference in means**
Complication	**Mean**	**95% Confidence interval**		**Mean**	**95% Confidence interval**		
Conceptions	709,736	709,634	709,838		N/A		
Ectopic pregnancies	10,706	10,703	10,710	10,694	10,689	10,699	12
Miscarriage	43,004	42,993	43,015	42,971	42,963	42,980	33
Placental abruption	2,443	2,442	2,444	2,438	2,437	2,439	5
Placenta previa	4,087	4,085	4,090	4,079	4,078	4,080	8
Pre-eclampsia	12,365	12,360	12,370	12,321	12,316	12,325	44

Figure 9.1: Kernel density plots for bootstrapped population mean estimates of occurrences and ESIP model output for maternal complications during pregnancy



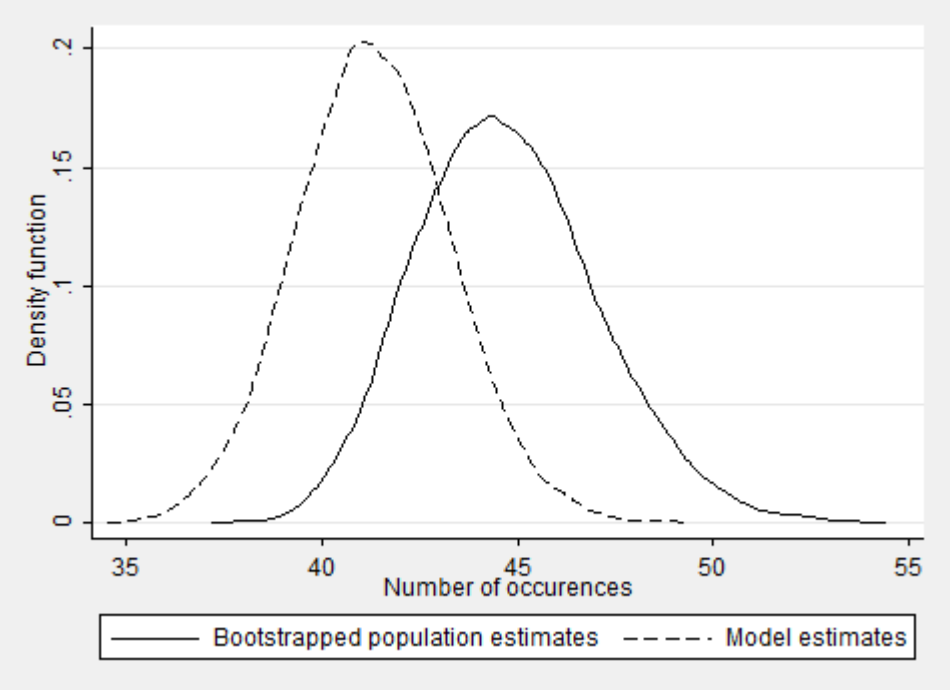
9.4.2 Maternal deaths

Table 9.3 reports the results of the bootstrapped population means and ESIP PSA predictions for the number of maternities and the number of deaths amongst mothers during pregnancy. The cohort for ESIP was set to 678,981. ESIP appeared to be conservatively estimating the number deaths during pregnancy, with a difference of four individuals between the population and ESIP means. The 95% CIs did not cross. From visual inspection of the Kernel distributions in Figure 9.2, both distributions appear to cross, although the peak of the model estimates appears to the left of the population estimates. The 95% CI was smaller in the ESIP estimates.

Table 9.3: Results of the non-parametric bootstrapping for ONS statistics of the number of maternities and deaths during pregnancy for England and Wales compared to the ESIP model predicted output

	Bootstrapped population estimates			**ESIP model PSA Output**			
Occurrence	**Mean**	**95% confidence interval**		**Mean**	**95% confidence interval**		**Differences in means**
Number of maternities	678,981	678,754	679,207		N/A		
Maternal deaths	45	45	45	41	41	41	4

Figure 9.2: Kernel density plots for bootstrapped population mean estimates of occurrences and ESIP model output for maternal deaths during pregnancy



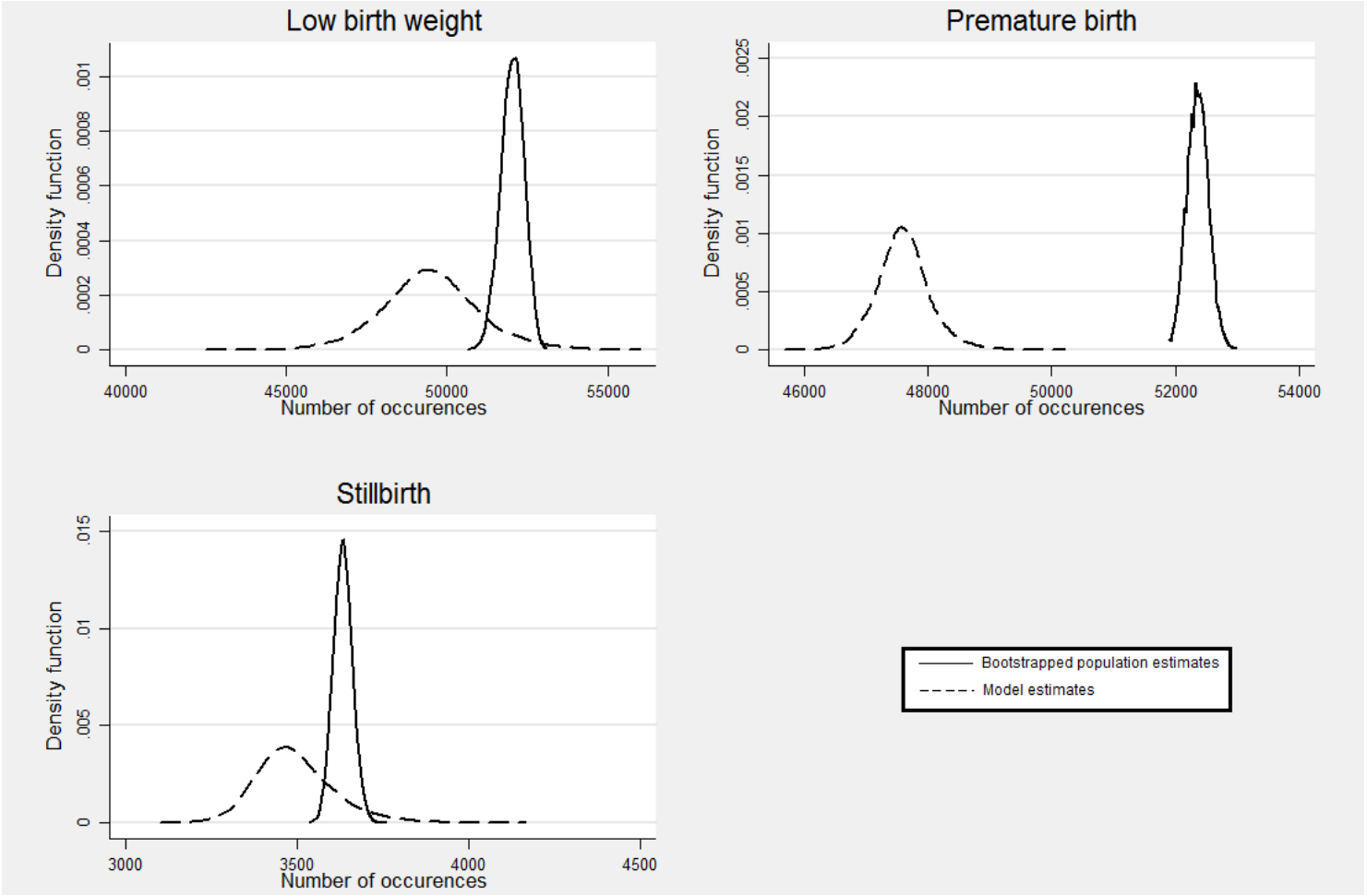
9.4.3 Infant birth outcomes

Table 9.4 reports the bootstrapped population mean estimate for infant birth outcomes and the results of the PSA analysis from ESIP. The cohort size in ESIP was set at 689,280. ESIP seemed to be conservatively estimating the number of adverse birth outcomes, with the means being lower than the bootstrapped population mean. The differences in the means were larger than compared to the previous analyses of maternal deaths and maternal complications. Visual inspection of the Kernel density distributions in Figure 9.3 suggested that the distributions overlapped for LBW and stillbirth, but for premature birth it was very clear that the model distribution was considerably to the left of the population mean distribution. The visual inspection also demonstrated that the distributions for all three birth outcomes were more spread out compared to the population estimates, with the 95% CIs being 4.24 times, 2.46 times, and 4.11 times larger than the population CIs for LBW, premature birth, and stillbirths respectively.

Table 9.4: Results of the non-parametric bootstrapping for ONS statistics of birth outcomes for infants in England and Wales compared to the ESIP model predicted output

	Bootstrapped population estimates			ESIP model PSA output			
Birth outcome	**Mean**	**95% confidence interval**		**Mean**	**95% confidence interval**		**Differences in mean**
Number of conceptions	689,280	689,049	689,511		N/A		
LBW	52,046	52,039	52,052	49,483	49,453	49,513	2,563
Premature births	52,365	52,362	52,369	47,606	47,597	47,614	4,759
Stillbirths	3,634	3,634	3,635	3,493	3,491	3,495	141

Figure 9.3: Kernel density plots for bootstrapped population mean estimates of occurrences and ESIP model output for infant birth



9.5 Discussion

This chapter reports a validation exercise for the within-pregnancy components of ESIP. Using non-parametric bootstrapping to determine a CI and distribution for the population mean number of complications/birth outcomes, this was compared with the output from ESIP's PSA to determine whether the output from ESIP appears to be a close approximation. To the author's knowledge, this has never been done before for an economic model. However, the bootstrapped population estimates are based upon relatively constrained data, especially premature birth, which may not represent the true population mean for these conditions.

9.5.1 Maternal complications within-pregnancy

The MWPC of ESIP seemed to produce very close estimates to the population for all the foetal loss and pregnancy-associated complications. Visual inspection of the comparative plots between the MWPC estimates and the population distribution suggested that the MWPC was producing reasonable estimates of occurrences which closely matched and overlapped with the population distribution. There were small differences in the means between ESIP and the population, the biggest difference being for pre-eclampsia (absolute difference of 44). However, the MWPC generated slightly conservative estimates for all within-pregnancy complications. For all conditions except ectopic pregnancy, the MWPC had a slightly smaller 95% CI compared to the bootstrapped population estimate, suggesting the MWPC had captured most, but not all, of the uncertainty within the population mean. For ectopic pregnancy, the 95% CI was wider in the MWPC output than the population estimate, suggesting that the parameters include a greater degree of uncertainty than in the population. One explanation is the uncertainty associated with the odds ratio for ectopic pregnancy. The impact of this greater uncertainty on the overall output for the ESIP model is unclear. Furthermore, the author cannot offer any explanation for the conservative estimates for the number of complications.

9.5.2 Death during pregnancy

The MWPC also seemed to produce conservative estimates for the number of maternal deaths during pregnancy. There was slightly less uncertainty in the MWPC estimates compared to the

population estimates, suggesting that the MWPC was capturing most but not all of the uncertainty around the number of deaths during pregnancy. From the visual inspection of the Kernel density plots, the distributions did overlap, though the MWPC distribution was to the left of the population distribution. One possible explanation for this is that the MWPC slightly underestimates the number of women who suffer a complication during pregnancy, and since suffering from most within-pregnancy complications is likely to increase the risk of death during pregnancy; this could be causing the MWPC to slightly underestimate the number of deaths during pregnancy.

9.5.3 Birth outcomes for the infant at the end of pregnancy

There appeared to be a greater difference between the IWPC predicted occurrences and the bootstrapped population estimates. For premature birth, LBW, and stillbirth, the IWPC appeared to generate consistently lower estimates of the number of occurrences. Differences in the means were a lot larger than the within-pregnancy maternal complications, with the ESIP output for LBW being 2,563 less than the population estimate, 4,759 for premature birth output, and 141 for the stillbirth output. However, for LBW and stillbirth the distributions did cross, while for premature birth, they did not. One explanation for the differences could be that the data used for determining whether a birth was premature or not comes from only one year of HES data [150], which could mean that either the year used was not representative of premature births (i.e. the number of premature births 2012-2013 was low in comparison to other years), or the prevalence of premature birth may be different in HES data compared to ONS estimates. Unfortunately, HES data reporting gestation length and complications is not available for any other year, and ONS data on prematurity is quite limited, therefore it is not possible to compare the 2012-2013 year with other years. Better estimates may be published in the future.

The visual inspection of the Kernel density plots did demonstrate that the distributions for the IWPC appear to be a lot flatter and more spread out. This suggests that there would appear to be a great deal of uncertainty in the prediction of birth outcomes. While the author can offer no explanations as to the cause of the uncertainty around premature birth, it is possible that the conservative estimates for stillbirth and LBW are caused by inaccuracy in the estimates of premature births, since the IWPC assumes that birth weight and stillbirth are related to premature birth. Therefore, if the IWPC is underestimating the number of premature births, it would seem sensible that the IWPC would be producing low estimates of LBW and stillbirths. If improved data for premature birth could be identified, then the estimates of LBW and stillbirth might improve. The conservative estimates of

infant birth outcomes suggest that ESIP is underestimating the healthcare costs associated with these outcomes. Furthermore, since the ICERs reported by the IWPC are directly linked with these values, it would seem to suggest that ESIP is reporting ICER values that are potentially too high. This could mean that ESIP is not capturing accurately the value for money of cessation interventions, and this could be leading to incorrect policy decisions, however the author cannot determine to what extent this may be an issue.

9.5.4 Implications of the validation exercise

The conservative estimates of the number of complications and maternal deaths estimated by the MWPC would suggest that the associated costs would also be conservatively estimated, while the associated QALYs would be slightly overestimated (fewer women receive a the utility loss associated with a complication/death), signifying that there might be a slight discrepancy in ESIP's output. For maternal death, if ESIP is calculating that too many mothers survive to the end of pregnancy, this could be inflating the health related benefit at the end of pregnancy. This could impact on the lifetime modelling conducted based upon the MWPC results (e.g. the MWPC over estimates the number of women who are alive at the end of pregnancy which is used as the cohort size in the lifetime model), potentially producing exaggerated health benefits. This in turn could lead to ESIP producing ICERs which are very low, and that in reality the ICER for cessation interventions should be higher. Hence, this could in turn lead to incorrect policy decisions being made based upon the results of this model. However, the differences for both complications and maternal deaths are relatively small; therefore this may not be an important issue for ESIP or the policy maker.

The IWPC also appears to be potentially underestimating the healthcare costs associated with birth outcomes. Because of this, it is likely that the estimates of value for money generated by ESIP are also conservatively estimated, suggesting that the ICERs calculated by the IWPC are too high. However, there is also an additional implication. For LBW and stillbirth, it is clear that there is a large amount of uncertainty, with the IWPC producing a distribution which has a much larger spread compared to the population distribution. It is unclear what impact this has on the overall healthcare costs associated with these conditions, as it could be both under- and overestimating these costs. However, it does suggest that ESIP is introducing a greater amount of parameter uncertainty into the evaluation than can be expected in the population, which would suggest that ESIP is adding to the degree of decision uncertainty regarding whether cessation interventions are cost-effective. This could be an issue to policy makers, however the author is unable to determine as to which direction

in terms of cost-effectiveness this greater parameter uncertainty impacts. If ESIP is overestimating the number of iterations that are cost-effective, then the policy maker will be fed an inflated estimate as to the probability of the intervention being cost-effective. However, if ESIP underestimates the number of iterations that are cost-effective, then the policy maker will be given an undervalued probability that the intervention is cost-effective.

These results would imply that the output from the IWPC should be treated with some caution, since these discrepancies between the IWPC and the population data appear to exist; however, without better data available with which to better parameterise the IWPC, this problem is unlikely to be solved.

9.6 Summary

This chapter demonstrates a validation exercise of comparing the output of the within-pregnancy components as generated by running a PSA when the ESIP is attempting to replicate the population distribution as generated by non-parametric bootstrapping. The results suggest that the MWPC is slightly conservative in its estimates of within-pregnancy complications and maternal deaths, however the differences in the means are very small, and the PSA output seems to match the population distributions closely, suggesting that we could consider the MWPC as valid and accurately capturing the cost-effectiveness of within-pregnancy cessation. Conversely, our results suggest that the IWPC seems to be poor at predicting birth outcomes when the PSA is compared to the population distribution, with large differences in the means, and the ESIP distributions being much wider than the bootstrapped population distribution. This would suggest that the IWPC estimates could be incorrect, and hence the estimates of the cost-effectiveness should be treated with caution. The next chapter demonstrates the validity of the overall ESIP model, and how it can be used to produce an evaluation of a within-pregnancy cessation intervention.

Chapter 10: Using ESIP to evaluate the SNAP intervention

10.1 Introduction

The previous chapters of this thesis have described the construction and parameterisation of the ESIP model; however, before ESIP can be utilised by the research community, it must be determined that it produces valid estimates of the cost-effectiveness of cessation interventions during pregnancy. To demonstrate this validity, ESIP has to be programmed and then allowed to perform an analysis on an intervention, for which there is already some evidence of cost-effectiveness. A recently published evaluation of a cessation intervention is the SNAP trial [123], which investigated the effectiveness and cost-effectiveness of NRT compared to placebo patch when given to pregnant women. This chapter reports the results use of SNAP data as a validation exercise for the ESIP model.

10.2 The SNAP Trial

10.2.1.1 Brief background to the SNAP trial

A detailed report of the SNAP trial was published by Cooper et al. [123] In brief; the SNAP trial was a Health Technology Assessment Programme-funded study investigating the efficacy and safety of NRT within pregnancy. It was conducted in seven antenatal hospitals in the Midlands and North-West of England, recruiting between May 2007 and February 2010. The objectives of the trial were:

- To compare the effectiveness and cost-effectiveness of NRT and placebo patches for achieving biochemically validated smoking cessation at delivery
- To compare the effects of maternal NRT and placebo patch use during pregnancy on the behaviour, development, and disability among infants at two years of age.

The trial design was a randomised, placebo-controlled, double-blinded, parallel group Phase IV trial with follow up at four weeks after randomisation; delivery and at six months; one year; and two years post-delivery. Randomisation was stratified by centre using a computer-generated sequence. The inclusion criteria for the trial were women between 12 and 24 weeks gestation who reported smoking at least five cigarettes daily, with an exhaled carbon monoxide reading greater than or equal to eight parts per million. The primary outcome measures were biochemically validated point

prevalence and prolonged abstinence at four weeks post-randomisation and delivery, and self-reported point prevalence and prolonged abstinence at six months, one year and two years postpartum. Secondary outcome measures included the absence of impairment amongst infants aged two years, the cost per quitter, and EQ-5D at six months. Statistical analyses were performed using an intention to treat analysis, with all recruited women who were lost to follow-up or excluded due to miscarriage/abortion treated as smokers.

10.2.1.2 Interventions included in the SNAP trial

The only difference between the control and experimental groups was that the experimental group received a four week supply of 15mg/16 hour NRT transdermal patches, whereas the control group received visually identical placebo patches which did not contain NRT. Both the control and experimental group received the following:

- At enrolment; counselling covering cognitive and behavioural changes was delivered by research midwife for up to one hour, with the self-help manual "The SNAP trial's guide to stopping smoking during pregnancy". All participants were asked to set a quit date within two weeks, and to start using the supplied patches on their quit date.
- Telephone behavioural support was delivered by research midwives on the participants' quit date, and at three days and one month afterwards.
- Four weeks after the quit date, those biochemically validated as abstinent were offered a further four weeks' supply of patches. Research midwives also offered a further face-to-face counselling session at this follow up point, which focused on reinforcement of earlier sessions and ways to avoid relapse.
- In addition, women could request further cessation support from both research midwives and local NHS Stop Smoking Services; however, this support was guided by the manual mentioned above.

10.2.1.3 Brief summary of the SNAP trial results

The trial recruited 1050 women, with 521 in the experimental group and 529 in the control group. The 1050 pregnancies resulted in 1034 live births (24 of which were twins), five miscarriages, seven

stillbirths, one elective termination, one missed abortion, and 14 where birth outcomes were unknown. There was no significant difference in rates of adverse events between the two groups. The validated cessation rate at delivery was 9.4% for the experimental group and 7.6% in the placebo group; therefore NRT was calculated to have an odds ratio for increased cessation of 1.26 (95% CI 0.82 to 1.96), suggesting it was not statistically significant at aiding cessation at delivery. However, there was a significant increase in abstinence at four weeks post quit date, with abstinence rates of 21.3% versus 11.7% in the experimental and control groups respectively (odds ratio 2.05, 95% CI 1.46 to 2.88). There was no significant difference in abstinence at the three follow-ups up to two years postpartum. Furthermore, there was no significant difference in the infant's reported respiratory problems at two years of age (odds ratio for symptoms in NRT versus placebo 1.30, 95% CI 0.97 to 1.74), but there was a significant difference in infants with 'no impairment' (odds ratio for symptoms in NRT versus placebo 1.40, 95% CI 1.05 to 1.86).

The total mean costs of delivering the intervention and healthcare resource use costs were approximately £91 higher in the experimental group. When including all women, the ICER was £4,929 per additional quitter, with a bootstrapped 95% CI of -£114,128 to £126,747. When restricting to singleton births only, the ICER was £4,156 per additional quitter, with a bootstrapped 95% CI of -£65,994 to £82,059. The authors concluded that the CIs demonstrated that there was a substantial degree of uncertainty associated with the SNAP intervention. Although EQ-5D data was collected for both groups, no cost-utility analysis using this data was performed due to the non-significant difference of EQ-5D scores and adverse birth outcomes between the control and intervention groups.

10.3 **Programming ESIP**

10.3.1.1 Programming the cohort to be included in ESIP

In order to perform an analysis of the SNAP intervention, ESIP requires some programming. Firstly, some basic details of the cohort of the women included within the trial are required. These can be found in Table 10.1.

Table 10.1: Basic details for the cohort of women as programmed into ESIP

Parameter	Value
Cohort size	1050
Year of giving birth	2008
Age of mother when giving birth	26

The cohort size was determined by the number of women included within the trial (n=1050). Year of giving birth was programmed at approximate mid-point of recruitment. The trial recruited for 34 months (May 2007 to February 2010), which suggests the mid-point of recruitment was September-October 2008. Therefore 2008 was used as the base year for the analysis. Furthermore, the mean age of the cohort of women within the trial was 26 years, and there was no significant difference in mean age between the experimental and control groups (26.4 versus 26.2 respectively).

10.3.1.2 Programming the SNAP intervention

The delivery quit rates reported by the control and experimental groups were entered into the ESIP programming sheet. The Beta distribution was fitted using the method of moments (see section 1.6.10. Details can be found in Table 10.2.

Table 10.2: Control and experimental groups' abstinence rates at the end of pregnancy with associated parameters for the fitting of the Beta distribution

Trial group	Proportion abstinent at end of pregnancy	Beta distribution parameters	
		α	β
Control	.076	7.6	92.4
Experimental	.094	9.4	90.6

The SNAP trial report also estimates the costs associated with delivering both the control and experimental intervention. These were estimated with mean (standard error) as £47.75 (19.03) and £98.31 (35.21) in 2009-2010 prices. However, ESIP uses cost data at 2011-2012 prices; therefore the mean cost of both interventions was inflated using the Hospital and Community Health Services (HCHS) Pay & Price Index [89], using the inflation index 1.0518. The standard error was not inflated

as this is a measure of the spread of the costs and therefore inflating the standard error would skew the associated uncertainty. The Gamma distribution was fitted to the control and experimental costs, and the details can be found in Table 10.3.

Table 10.3: Cost of control and experimental interventions in 2011-2012 prices, with associated parameters for the fitting of the Gamma distribution

Trial group	Mean cost (£)	Standard error (£)	Gamma distribution parameters	
			α	β
Control	50.22	19.03	6.9643	7.2111
Experimental	103.40	35.21	8.6240	11.9898

10.3.1.3 Perspective of analysis

As has been outlined in earlier chapters describing ESIP and required by NICE guidance, an NHS and PSSRU perspective was adopted. [36] All costs were reported at 2011-2012 prices. All costs and QALYs were discounted at a base rate of 3.5%, as recommended by NICE guidance. [36] All other parameters within ESIP remained as described in earlier chapters of this thesis. ESIP was not programmed to use specific trial postpartum relapse rates, so used the general postpartum relapse estimates as reported in Chapter 4. To allow the combination of the results for the maternal and infant components, the cost of the control/experimental interventions were not included in the infant within-pregnancy and childhood components. Hence, the infant models were used to generate expected costs and gains which could then be combined with the results from the components representing the mother.

Initially, a deterministic analysis was performed. One-way sensitivity analyses were performed under the following scenarios:

- Varying the quit rate of the control group between 3.8% and 15.2%
- Varying the quit rate of the experimental group between 4.7% and 18.8%
- Varying the cost of the control group intervention between £25.11 and £100.44
- Varying the cost of the experimental group intervention between £51.70 and £206.80

To determine the complete impact of uncertainty, all parameters with which uncertainty was associated were varied by performing a probabilistic sensitivity analysis (PSA) with 10,000 iterations.

Both results from the deterministic and probabilistic analyses are presented from a within-pregnancy time horizon for the mother, and the combination of both mother and infant. Additionally, a time horizon of age 100 years is presented for the mother and age 15 years for the infant, as well as the combination of both sets of post-delivery modelling estimates for mother and infant.

10.4 **Results**

10.4.1 Deterministic

Table 10.4, Table 10.5, and Table 10.6 report the results for the deterministic analysis both within pregnancy and post-delivery for the mother, infant, and combined mother and infant.

Table 10.4: Results of the deterministic analysis for the mother

MATERNAL: END OF PREGNANCY			
	Control	Experimental	Incremental
Number of quitters	80	99	19
Quit rate (%)	7.60	9.40	1.80
Expected Cost per mother (£)	2,670.53	2,724.68	54.14
Expected QALYS per mother	0.6336	0.6343	0.0007
		Incremental cost per QALY (£)	77,209.47
		Incremental cost per quitter (£)	3,008.00
MATERNAL: LIFETIME			
	Control	Experimental	Incremental
Percentage of cohort still alive	19.33	19.35	0.02
Percentage of cohort with morbidity	49.84	49.82	-0.03
Expected cost per mother (£)	£9,743.70	£9,789.26	45.56
Expected life Years	59.7254	59.7372	0.0117
Expected QALYS	21.4208	21.4269	0.0061
		Incremental cost per life year gained (£)	3,882.06
		Incremental cost per QALY (£)	7,462.57
		Incremental cost per quitter (£)	2,531.14

Table 10.5: Results of the deterministic analysis for the infant

INFANT: END OF PREGNANCY			
	Control	Experimental	Incremental
Number of infants alive	939	939	1
Number of infants lost (ectopic, miscarried, stillborn)	111	111	-1
Number of premature births	77	77	0
Number of infants with low birth weight	118	117	-1
Number of all adverse live births	113	113	0
Number of all adverse pregnancy outcomes	224	223	-1
Expected cost per infant (£)	2,031.67	2,030.31	-1.37
INFANT: AGE 15			
	Control	Experimental	Incremental
Percentage of cohort alive	88.84	88.89	0.06
Percentage of cohort with asthma	29.28	29.18	-0.11
Expected cost per infant (£)	£2,527.76	£2,525.06	-2.70
Expected life years per infant	13.3332	13.3418	0.0086
Expected QALYs per infant	10.1241	10.1311	0.0069

Table 10.6: Results of the deterministic analysis for combined mother and infant

COMBINED MOTHER AND INFANT: END OF PREGNANCY			
	Control	Experimental	Incremental
Expected cost (£)	4,702.21	4,754.98	52.78
Expected QALYs	0.6336	0.6343	0.0007
	Incremental cost per quitter (£)		2,932.10
	Incremental cost per QALY (£)		75,261.24
COMBINED MOTHER AND INFANT: POST-DELIEVERY			
	Control	Experimental	Incremental
Expected cost (£)	12,271.47	12,314.33	42.86
Expected life years	73.06	73.08	0.0204
Expected QALYs	31.5449	31.5579	0.0130
	Incremental cost per quitter (£)		2,381.37
	Incremental cost per life year gained (£)		2,104.60
	Incremental cost per QALY (£)		3,286.75

From the perspective of the mother, the SNAP intervention leads to a £54.14 increase in expected cost per mother within pregnancy, which decreases to £45.56 when considering the mother's lifetime. QALYs also increase under the SNAP intervention by 0.0007 by the end of pregnancy and 0.0061 over the mother's lifetime. ESIP also suggests that the SNAP intervention increases the number of women alive at age 100 by 0.02% and reduces the number of women with co-morbidities by 0.03%. Considering the number of quitters as our primary objective, as the deterministic model suggests that if the willingness to pay per quitter gained was £3,008.00, we could consider the SNAP intervention value for money by the end of pregnancy. However, if the primary outcome was QALY gained, then by the end of pregnancy the willingness to pay required for the SNAP intervention to be considered cost-effective is £77,209.47 per QALY gained. The implication of these results can be found in the discussion.

For the infant, the SNAP intervention decreased the number of adverse pregnancy outcomes by one, due to a decrease in the number of infants being born with low birth weight. This suggested that by the end of pregnancy the SNAP intervention will have saved £1.37 per infant in healthcare costs compared to infants whose mothers only receive standard care. When considering the infants childhood up to the age of 15, the healthcare cost savings generated by the SNAP intervention are now £2.70 per infant. This is due to the 0.11% reduction in the number of children with asthma in the SNAP intervention group. Furthermore, more children are alive by age 15 in the SNAP intervention, and there is a 0.0069 gain in QALYs. No ICERs can be calculated for the infant results

because the cost of the intervention is not included within the infant model, and therefore the results are reproduced here for information.

Once the results for the mother and her infant have been combined, the SNAP intervention increases expected costs by £52.78 per pregnancy at the end of pregnancy and £42.86 per pregnancy when considering the mother's lifetime and infant's childhood. Expected QALYs also increased by 0.0007 per pregnancy within-pregnancy and by 0.0130 per pregnancy when including lifetime and childhood. ESIP estimated that the incremental cost per quitter was £2,932.10 within-pregnancy and £2,381.37 when including lifetime and childhood, which suggests that if the willingness to pay for an additional quitter was £2,932.10, then the SNAP intervention could be considered value for money. However, the incremental cost per additional QALY is £75,261.24 when only considering pregnancy, and £3,286.75 when including the longer term. This would suggest that the willingness to pay for an additional QALY would have to be at least £75,261.24 before the SNAP intervention could be considered value for money.

10.4.2 Sensitivity analyses

The results of the sensitivity analysis for the incremental cost per quitter, combining costs associated with both the mother and infant can be found in Figure 10.1 and Figure 10.2, covering both within pregnancy and lifetime/childhood time horizons.

Figure 10.1: Tornado plot demonstrating the effect of sensitivity analyses on incremental cost per quitter combining costs associated with both the mother and her infant within pregnancy

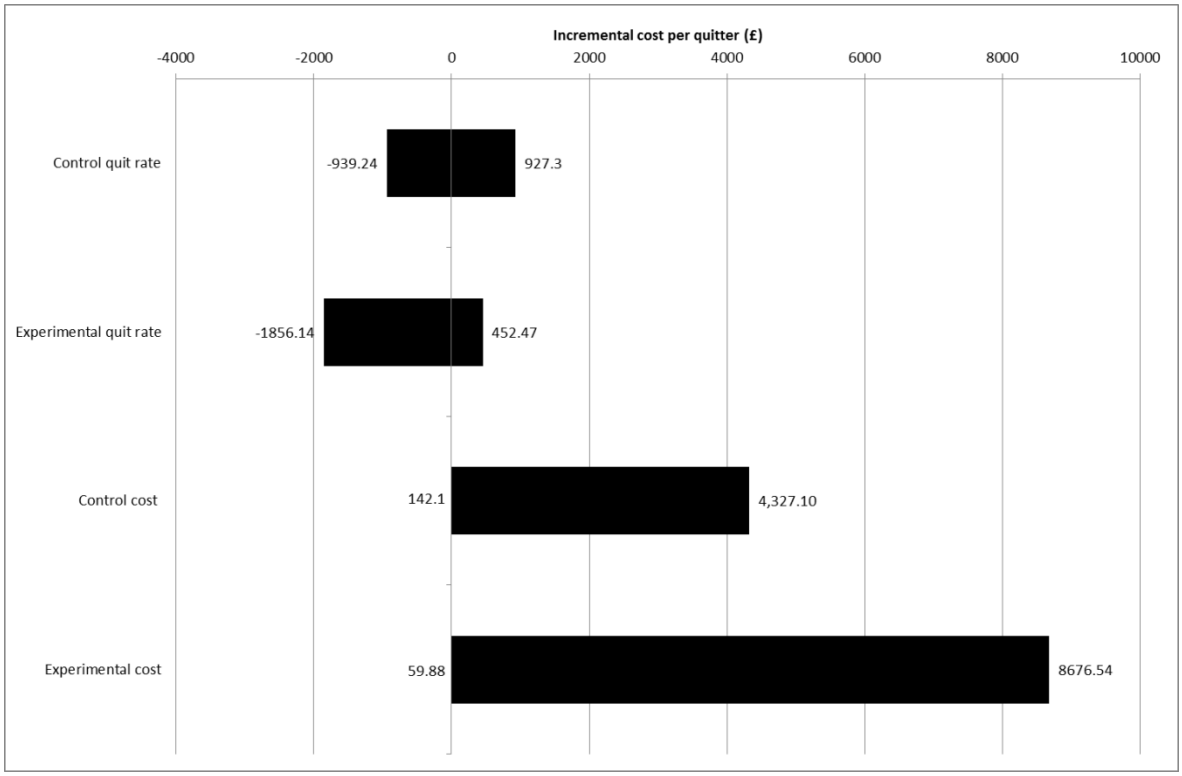
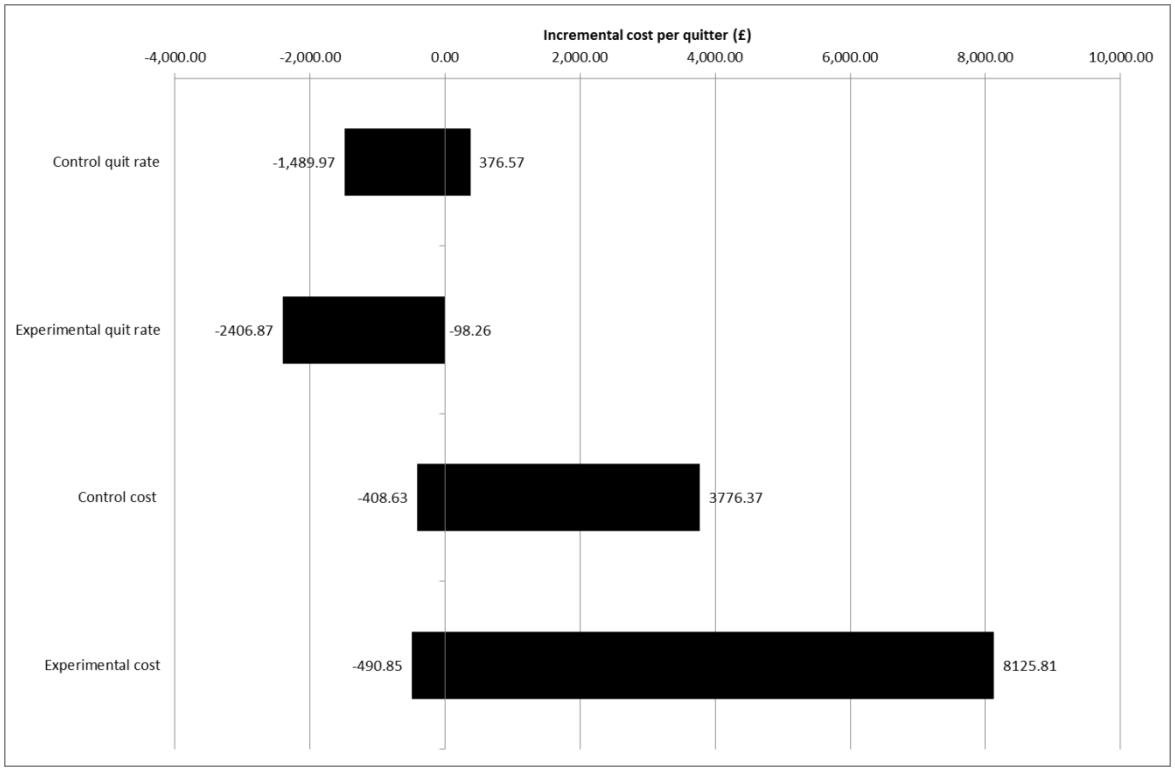


Figure 10.2: Tornado plot demonstrating the effect of sensitivity analyses on incremental cost per quitter combing costs and outcomes associated for both the mother up to age 100 and her infant up to age 15



The ICER per quitter seems to be highly sensitive to the cost of the SNAP intervention, as varying this in the sensitivity analysis appeared to have the greatest impact on the ICER, followed by the cost of usual care. This would suggest that the ICER is more sensitive to changes in cost than it is to changes in quit rates. However, it is worth noting that the SNAP intervention was considered dominated by usual care when the control quit rate was 15.2% and the experimental quit rate was 4.7%, both within-pregnancy and including longer term outcomes. Conversely, it was only considered dominant when considering impacts across the lifetime and childhood once the experimental intervention quit rate was 18.8%, when the experimental intervention cost was £51.70, and the control intervention cost £100.44. The SNAP intervention never gained dominance when considering costs and outcomes up to the end of pregnancy under the sensitivity analyses. The same behaviour in ICERs was observed when considering the impact of the sensitivity analyses on the ICER per additional QALY, but there was a greater degree in variability in the ICER reported by ESIP. These results can be found in Figure 10.3 and Figure 10.4.

Figure 10.3:Tornado plot demonstrating the effect of sensitivity analyses on incremental cost per additional QALY combining costs associated with both the mother and her infant within pregnancy

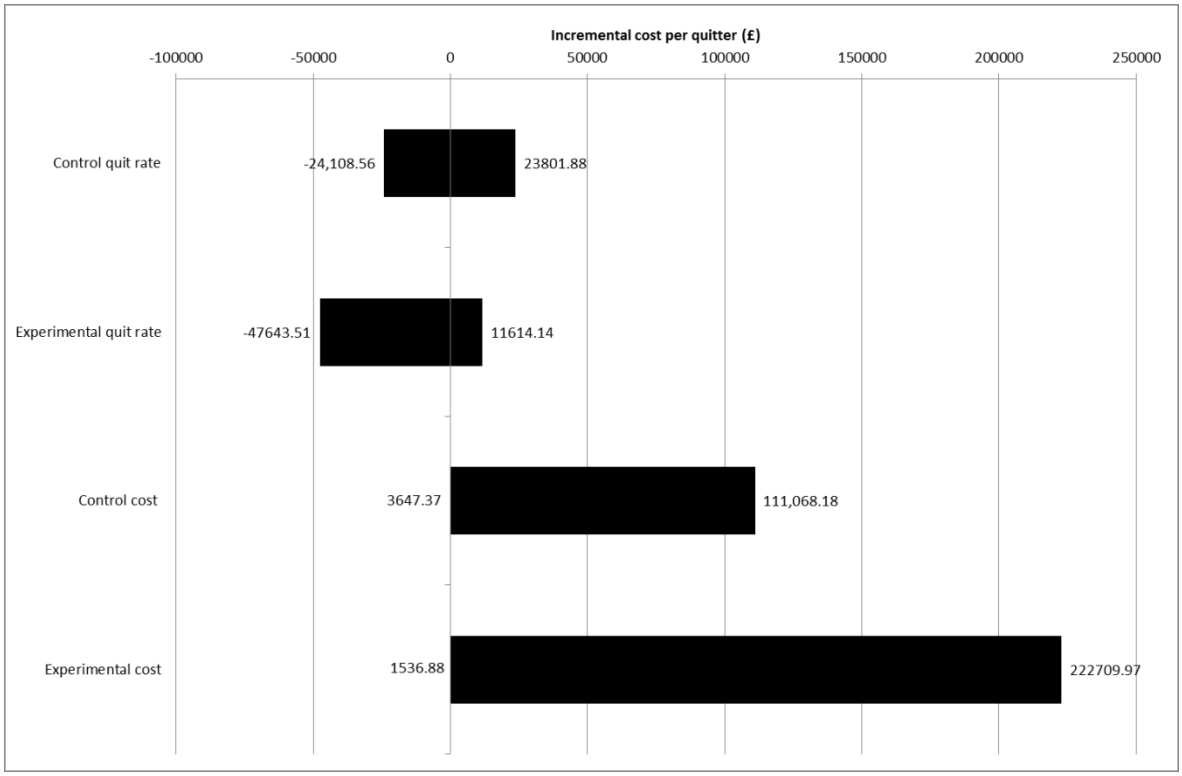
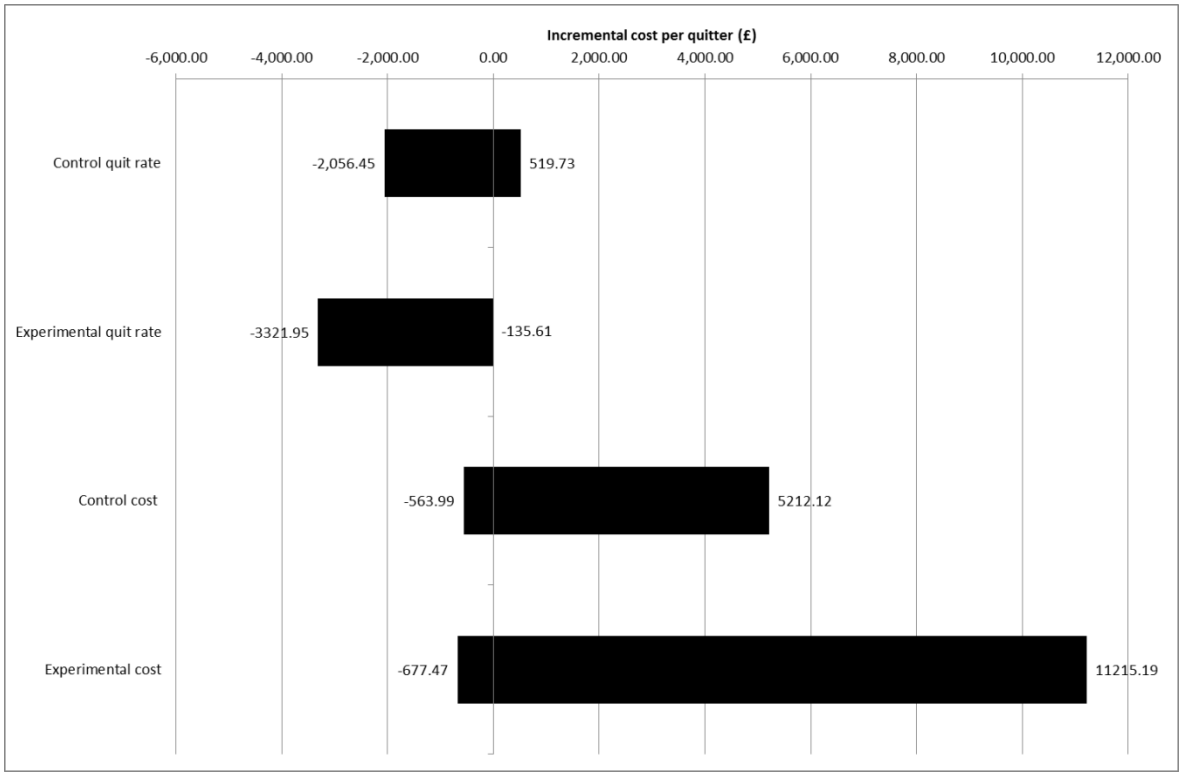


Figure 10.4: Tornado plot demonstrating the effect of sensitivity analyses on incremental cost per additional QALY combing costs and outcomes associated for both the mother up to age 100 and her infant up to age 15



10.4.3 Results from the probabilistic sensitivity analysis

To control for all parameter uncertainty within ESIP, a PSA was performed. Table 10.7 reports the results of this analysis for the mother both within-pregnancy and up to the age of 100 years, while Figure 10.5 and Figure 10.6 display the scatterplots for incremental costs versus incremental QALYs for up to the end of pregnancy and up to the age of 100 years.

Table 10.7: Results of the probabilistic sensitivity analysis for the mother both within-pregnancy and up to the age of 100 years

Maternal : End of pregnancy									
	Control			Experimental			Incremental		
	Mean	95% confidence interval		Mean	95% confidence interval		Mean	95% confidence interval	
Number of quitters	80	35	141	99	47	163	19	-61	99
Quit rate (%)	7.61	3.31	13.40	9.38	4.50	15.55	1.77	-5.83	9.43
Expected cost per mother (£)	2,674.28	1,685.27	3,948.78	2,728.85	1,743.73	4,002.67	54.57	-17.62	141.23
Expected QALYs per mother	.6334	.6158	.6482	.6341	.6165	.6489	.0007	-.0023	.0038
						ICER per QALY (£)	78,821.55	-499,122.85	653,852.19
					Probability cost-effective (WTP per QALY = £30,000)		.2813		
						ICER per quitter (£)	3,074.58	-19,334.68	25,232.53
Maternal: Lifetime									
	Control			Experimental			Incremental		
	Mean	95% confidence interval		Mean	95% confidence interval		Mean	95% confidence interval	
Cohort alive (%)	19.34	15.79	23.08	19.36	15.79	23.10	.01	-.06	.11
Cohort with morbidity (%)	49.86	47.22	52.49	48.80	45.79	51.68	-1.07	-2.61	-.05
Expected cost per mother (£)	9,752.69	8,348.22	11,373.29	9,800.32	8,390.51	11,434.72	47.63	-34.01	139.58
Expected life years	59.6992	58.9975	60.3852	59.7087	59.0029	60.3946	.0095	-.0392	.0709
Expected QALYs	21.4124	20.5295	22.1350	21.4175	20.5322	22.1400	.0051	-.0197	.0356
						ICER per life year gained (£)	5,010.11	-99,503.73	113,788.51
						ICER per QALY (£)	9,333.42	-100,896.65	111,433.37
					Probability cost-effective (WTP per QALY = £30,000)		.5933		
						Incremental cost per quitter (£)	2,683.41	-19,650.37	24,794.48

Figure 10.5: Scatterplot for incremental costs and incremental QALYs for the mother within-pregnancy with 95% confidence ellipse for the ICER

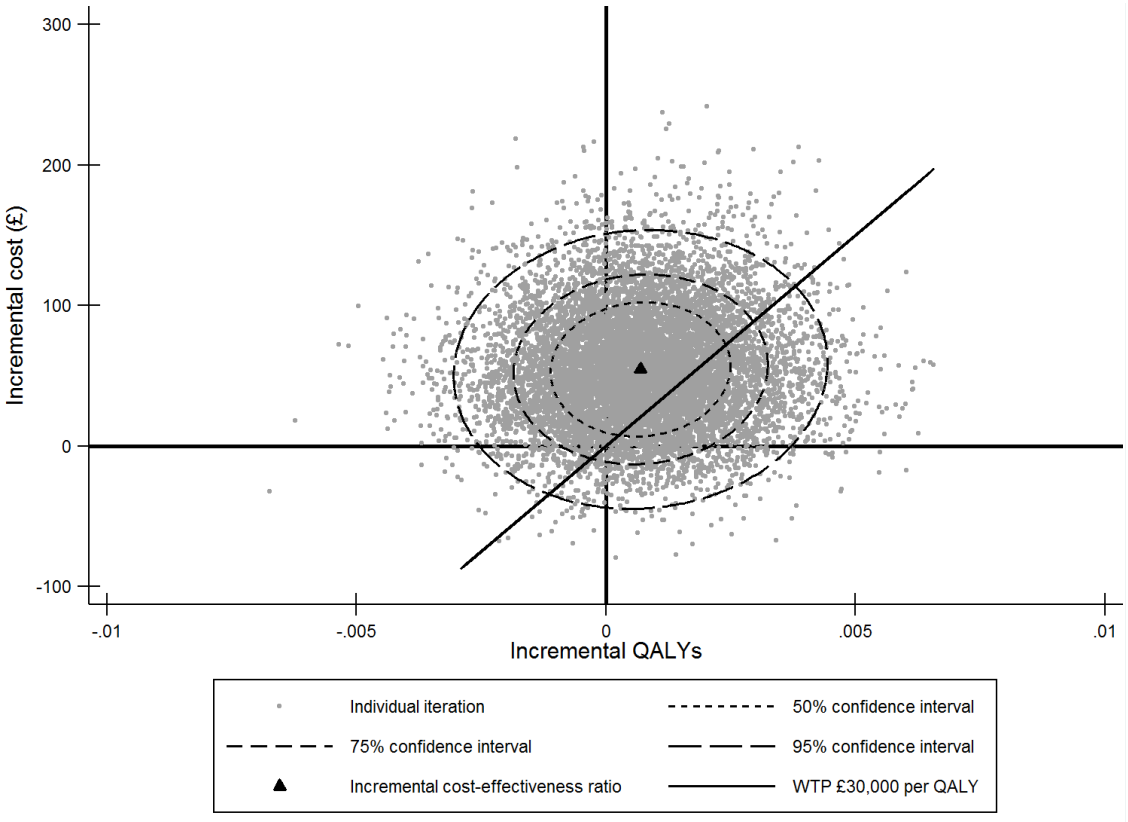
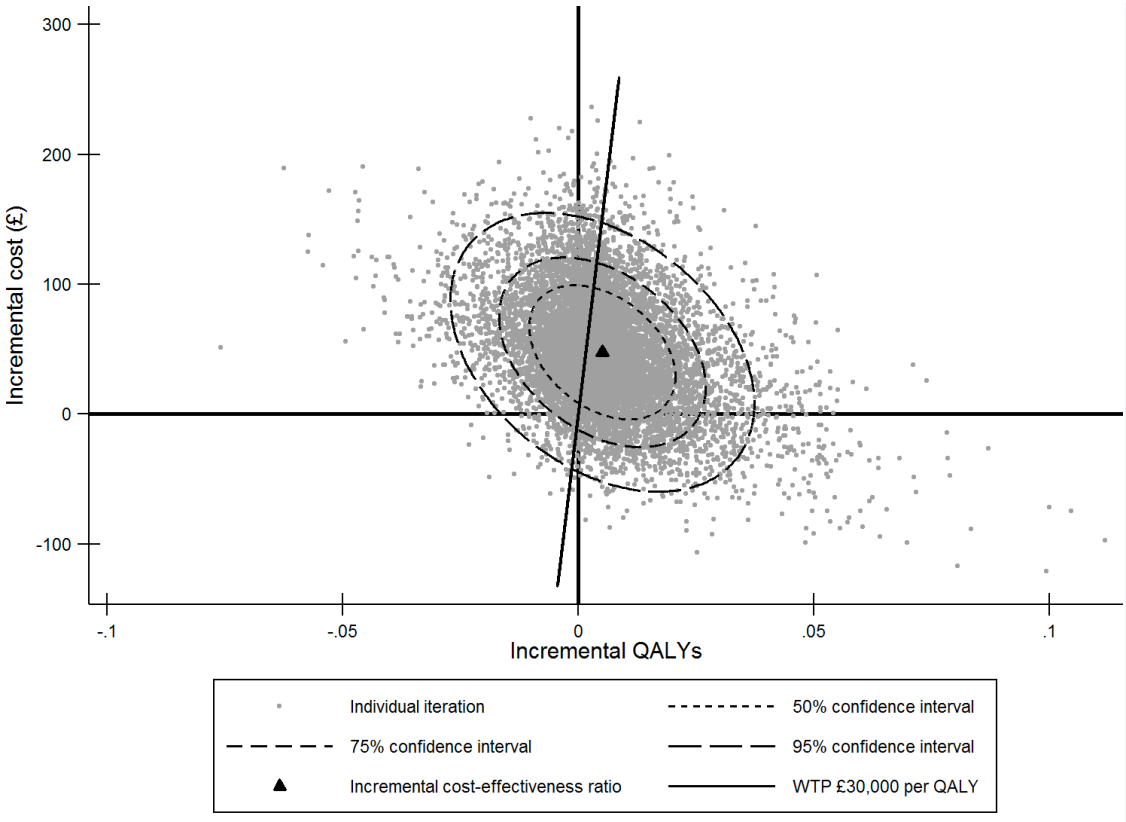


Figure 10.6: Scatterplot of incremental costs versus incremental QALYs for the mother up to age 100, with 95% confidence ellipse for the ICER



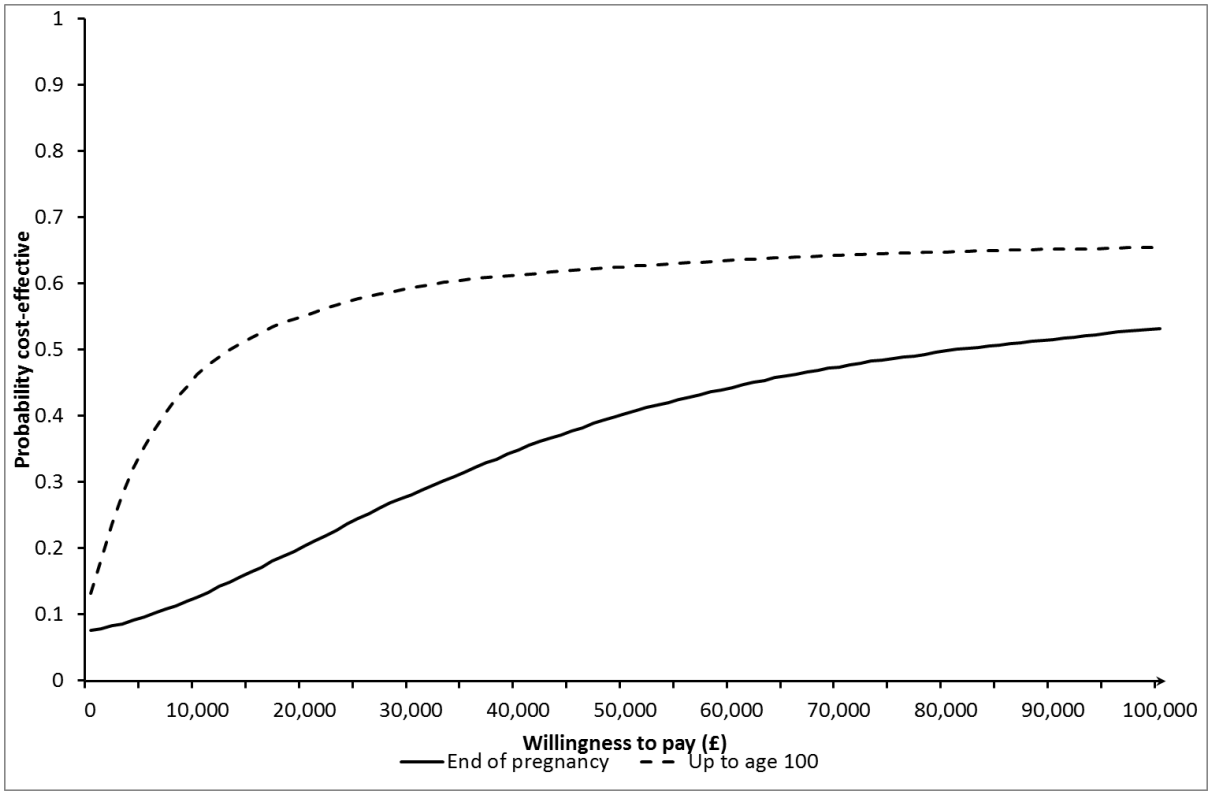
The results suggest that, assuming the primary outcome is the incremental cost per quitter, if we were willing to spend £3,074.58 to gain an additional quitter by the end of pregnancy, then the SNAP intervention could be assumed to be cost-effective. Extending this to the lifetime perspective reduces the ICER, demonstrating the impact of healthcare cost savings gained over the remaining life expectancy of the mother. However, the CIs cross zero, which suggests that there may be instances where the SNAP intervention is either dominated or dominant; unfortunately we cannot determine which from the ICER alone.

Both within pregnancy and up to the age of 100 years old, there is a significant difference in expected cost per mother, with a mean increase in cost of £54.57 within-pregnancy and £47.63 by the age of 100 years. Although there was weak evidence of increased QALYs both at the end of pregnancy and up to age 100, this difference was non-significant. Within pregnancy, the ICER was £78,821.55 per QALY (95% CI -£499,122.85 to £653,852.19), with a 28% probability of being cost-effective at a willingness to pay of £30,000 per incremental QALY. From the scatterplot in Figure 10.5, it can be clearly seen that the majority of the iterations lie within the north east quadrant of

the cost-effectiveness plane, but the 95% confidence ellipse suggests that there are more iterations where the SNAP intervention is dominated by usual care rather than the SNAP intervention dominating usual care. When extending the time horizon to age 100 years, the ICER decreased to £9,33.42 (95% CI -£100,896.65 to £111,433.37) with a probability of being cost-effective at the same willingness to pay of 0.5933. From the scatterplot in Figure 10.6, the majority of the iterations still remain in the north east quadrant of the cost-effectiveness plane, but the 95% confidence ellipse for the ICER crosses all four quadrants, suggesting a large amount of uncertainty in the ICER. Compared to the ICER per quitter, there was a greater degree of uncertainty in the ICER per QALY.

The cost-effectiveness acceptability curves can be found in Figure 10.7. The CEAC suggests that by the end of pregnancy, less than 10% of iterations save money. However, when extending it to the lifetime, this increased to approximately 15%. Nonetheless, the remaining the CEACs also suggest that by the end of pregnancy, even at a willingness to pay of £100,000, approximately 47% of iterations are not cost-effective, suggesting that around 47% of iterations do not offer any health benefit to the mother. When considering the remaining life expectancy of the mother, this is reduced to approximately 35%, suggesting that 35% of iterations do not offer any health benefit in the long term. This is also clearly demonstrated in the scatter plots in Figure 10.5 and Figure 10.6.

Figure 10.7: Cost-effectiveness acceptability curves for the mother at the end of pregnancy and over her lifetime



10.4.4 Probabilistic Sensitivity Analysis results for the infant

Within pregnancy, there is evidence to suggest that the SNAP intervention reduced the number of pregnancies lost (e.g. ectopic, miscarried, still born) and the number of infants born with low birth weight; however, the model did not report any significant difference between the experimental and control groups. Conversely, the model did suggest there was a significant difference in both the number of live births with an adverse outcome and the number of all adverse pregnancy outcomes.

The results of the PSA for the child can be found in Table 10.8. Although there was evidence that the SNAP intervention may have been cost-saving, there was no significant difference in healthcare costs between the experimental and control groups, both at the end of pregnancy and up to the age of 15 years. There also appeared to be a non-significant difference for all within-pregnancy outcomes, and the number of infants alive, number of infants with asthma, expected life years per infant, and expected QALYs per infant by the age of 15 years, although there was weak evidence that the SNAP intervention improved the outcomes associated with these metrics.

Table 10.8: Results of the probabilistic sensitivity analysis for the infant for both within-pregnancy and up to the age of 15 years

Infant: End of pregnancy									
	Control			Experimental			Incremental		
	Mean	95% confidence interval		Mean	95% confidence interval		Mean	95% confidence interval	
Number of live births	939	930	947	939	931	948	1	-2	3
Number of infants lost (ectopic, miscarried, stillborn)	111	98	125	111	98	124	-1	-3	2
Number of premature births	77	68	88	77	68	87	0	-2	1
Number of low birth weight	116	93	133	115	93	132	-1	-6	4
Number of adverse live births	114	101	128	113	101	127	0	-3	2
Number of all adverse pregnancy outcomes	225	209	242	224	209	241	-1	-6	4
Expected cost per infant (£)	2,012.95	533.69	5,171.93	2,011.64	530.38	5,178.05	-1.31	-16.67	11.15
Infant: Childhood (age 15 years)									
	Control			Experimental			Incremental		
	Mean	95% confidence interval		Mean	95% confidence interval		Mean	95% confidence interval	
Cohort alive (%)	88.84	88.00	89.62	88.89	88.08	89.67	.06	-.19	.31
Cohort with asthma (%)	22.53	17.32	28.31	22.47	17.40	28.10	-.06	-.55	.30
Expected cost per infant(£)	2,517.99	739.73	6,016.97	2,515.25	740.02	6,028.29	-2.75	-27.32	15.44
Expected life years per infant	13.3335	13.2086	13.4508	13.3421	13.2203	13.4584	.0085	-.0284	.0468
Expected QALYs per infant	10.1271	9.4576	10.3169	10.1340	9.4691	10.3221	.0069	-.0230	.0382

10.4.5 Results of the PSA when combining both the mother and her infant

Table 10.9 gives the results of the PSA when both mother and infant are combined, both up to the end of pregnancy and across lifetime/childhood, while Figures Figure 10.8 and Figure 10.9 give the scatter plots of incremental costs versus incremental QALYs.

Table 10.9: Results of the probabilistic analysis combining both the mother and infant for both within-pregnancy and lifetime/childhood

Combined mother and infant: End of pregnancy									
	Control			Experimental			Incremental		
	Mean	95% confidence interval		Mean	95% confidence interval		Mean	95% confidence interval	
Expected cost per pregnancy (£)	4,687.23	2,744.03	8,016.65	4,740.50	2,796.12	8,072.77	53.27	-20.93	141.57
Expected QALYs per pregnancy	.6334	.6158	.6482	.6341	.6165	.6489	.0007	-.0023	.0038
						ICER per quitter (£)	3,001.14	-19,360.13	25,094.05
						ICER per QALY (£)	76,933.87	-503,395.10	652,204.67
						Probability cost-effective (WTP per QALY = £30,000)	.2961		
Combined mother and infant: Lifetime and childhood									
	Control			Experimental			Incremental		
	Mean	95% confidence interval		Mean	95% confidence interval		Mean	95% confidence interval	
Expected cost per pregnancy (£)	12,270.68	9,836.44	16,005.78	12,315.26	9,866.23	16,038.76	44.88	-44.49	142.58
Expected life years per pregnancy	73.0327	72.3121	73.7324	73.0508	72.3315	73.7465	.0180	-.0640	.1096
Expected QALYs per pregnancy	31.5395	30.5222	32.3328	31.5515	30.5354	32.3426	.0120	-.0412	.0688
						ICER per quitter (£)	2,528.69	-19,835.35	24,554.82
						ICER per life year gained (£)	2,487.66	-22,262.49	26,323.59
						ICER per QALY (£)	3,746.22	-30,996.28	37,393.31
						Probability cost-effective (WTP per QALY = £30,000)	.6525		

Figure 10.8: Scatterplot of incremental costs versus incremental QALYs for combined mother and infant up to the end of pregnancy, with 95% confidence ellipse

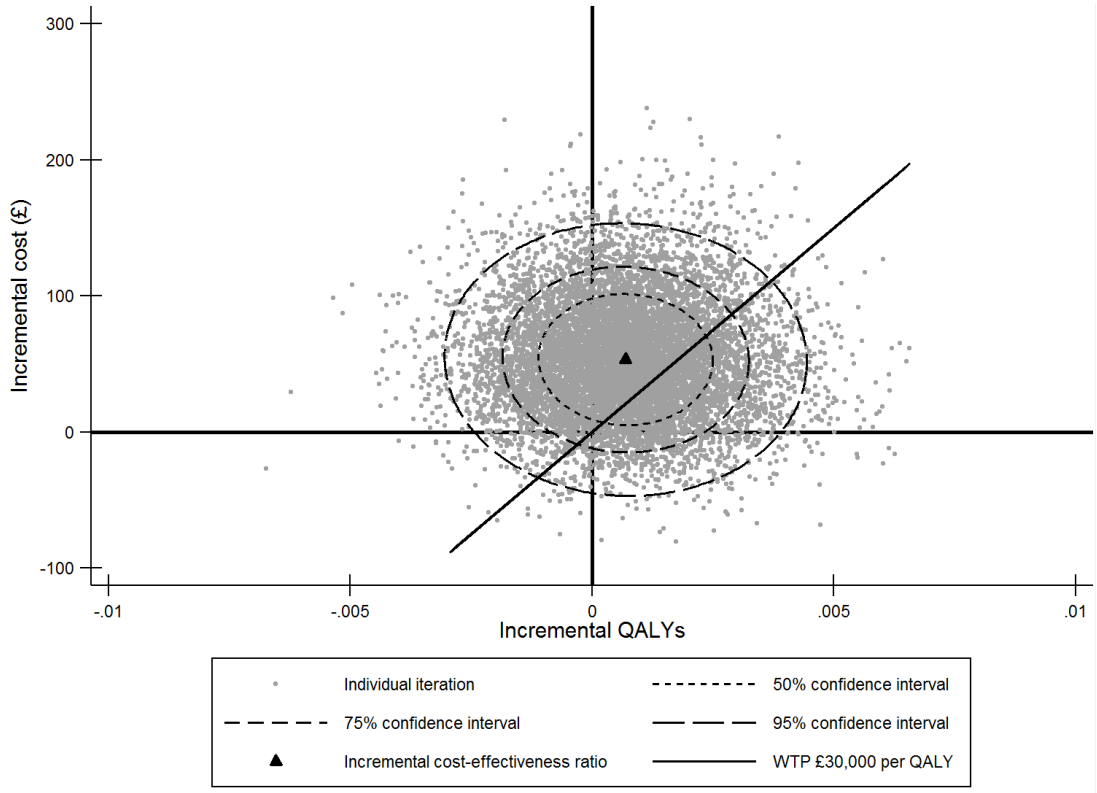
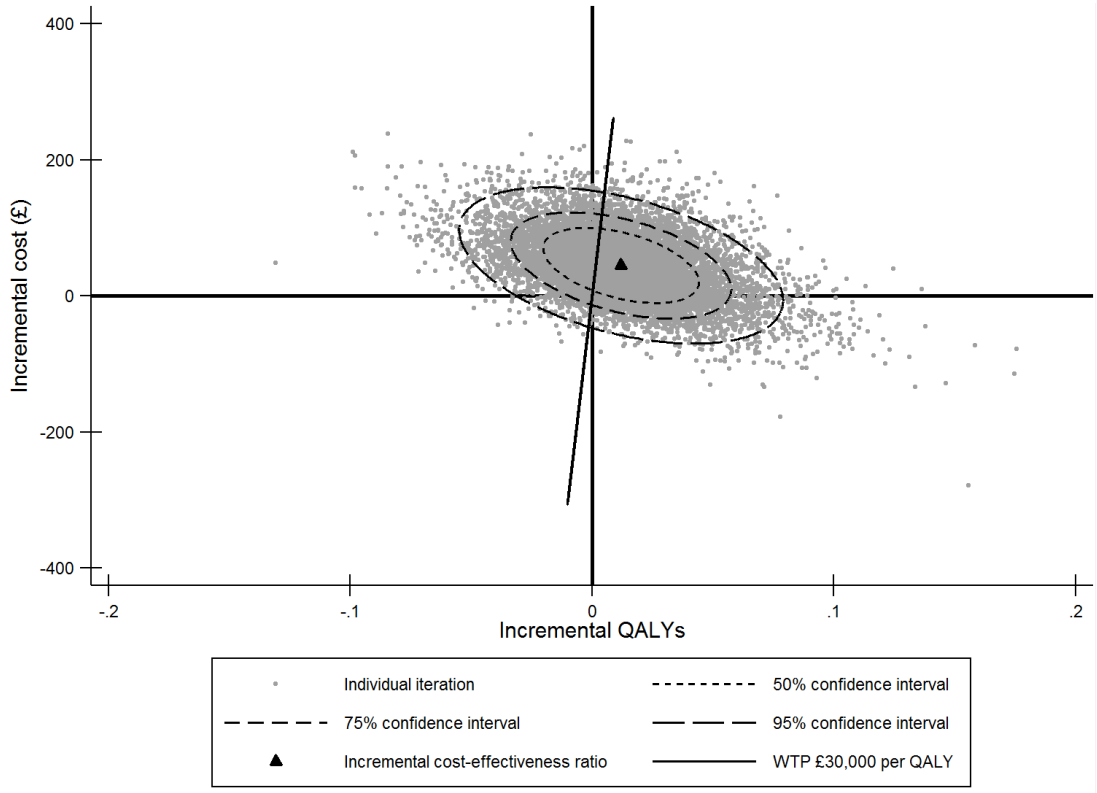


Figure 10.9: Scatterplot of incremental costs versus incremental QALYs for combined mother and infant up to age 100 years for the mother and age 15 years for the infant, with 95% confidence ellipse for the ICER

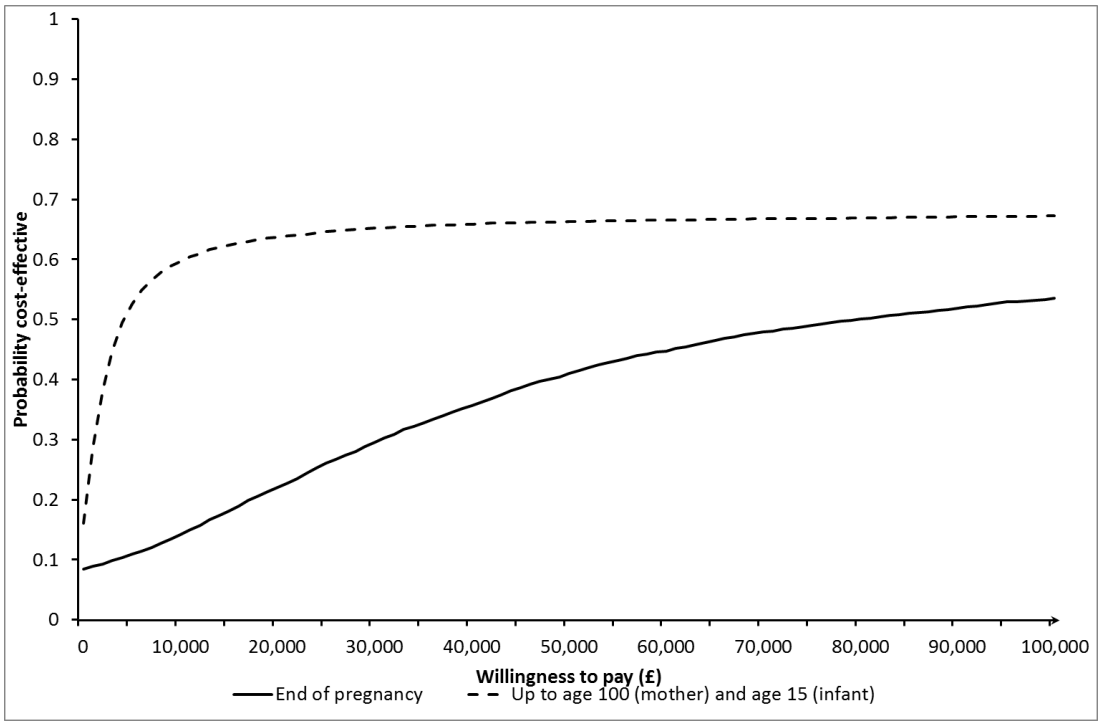


At the end of pregnancy, there was no significant difference in expected cost per pregnancy and expected QALYs per pregnancy between the control and experimental groups, although there was weak evidence of an increase in expected QALYs per pregnancy. When extended to include the lifetime for the mother and childhood for the infant, there was still no evidence of a significant difference in expected costs per pregnancy, expected life years per pregnancy, and expected QALYs per pregnancy. However, there was weak evidence of a decrease in expected costs per pregnancy and an increase in expected QALYs and life years per pregnancy, suggesting that the SNAP intervention was dominant, although the 95% CIs crossed zero, suggesting that there may be instances where the SNAP intervention is not dominant. The probability of the SNAP intervention being cost-effective was 0.6525 at a willingness to pay of £30,000 per incremental QALY. Within-pregnancy, the ICER per QALY was £76,933.87 (95% CI -£503,395.10 to £652,204.67); suggesting there was a great deal of uncertainty in the ICER at the end of pregnancy and that there may be instances where the SNAP intervention is dominant or dominated. This can clearly be seen in Figure 10.9 where the 95% confidence ellipse crosses all four quadrants along with the iterations from the PSA. The probability of the SNAP intervention being cost-effective at the end of pregnancy was 0.2961 at a willingness to pay of £30,000 per incremental QALY. Figure 10.8

suggests that the majority of the iterations are to the right hand side of the vertical axis, however the 95% confidence ellipse crosses all four quadrants suggesting there is a large amount of uncertainty in the ICER.

The CEACs are represented in Figure 10.10 and suggest that at the end of pregnancy, just under 10% of iterations offered cost-savings, which increased to approximately 15% when extending to the lifetime and childhood time horizons. Furthermore, the CEACs suggest that approximately 50% of iterations by the end of pregnancy and approximately 32% of iterations when incorporating lifetime and childhood offered no health benefit to either the mother or infant, or both. This can also be seen in the scatter plots with several iterations being to the left of the vertical axis.

Figure 10.10: Cost-effectiveness acceptability curves for combined mother and infant up to end of pregnancy and age 100 years for the mother and age 15 years for the infant



10.5 **Discussion**

The ESIP model has been used to evaluate the SNAP intervention, performing both deterministic and probabilistic analyses. Our deterministic results suggest that for the mother, within pregnancy, the SNAP intervention may be seen as not value for money if there is only a willingness to pay £30,000 per incremental QALY. [36] However, when extending the time horizon to include the remaining lifetime of the mother, the SNAP intervention becomes cost-effective. The addition of healthcare costs and benefits associated with the infant decreases the ICERs in both time horizons, but does not change the overall decision. Our probabilistic results further support the deterministic analysis for the mother; however the probabilistic results suggest that, when including infant outcomes within pregnancy, the SNAP intervention becomes cost-effective, which is contrary to the deterministic results. However, the estimated 95% CIs for the ICER per QALYs were very wide at the within-pregnancy time horizon, and therefore demonstrate there is a great deal of uncertainty in these results.

10.5.1 Limitations of this analysis

One difference between the SNAP trial and any analyses undertaken using ESIP is that the SNAP trial recruited women later in gestation, whereas the ESIP model considers the whole gestation period. This means that the SNAP trial may not include women who suffered an ectopic pregnancy or miscarried before they could be identified for recruitment; however they will be included within the ESIP model. Henceforth it could be argued that ESIP is modelling a slightly different pregnant population compared to the estimates generated by the SNAP trial. This can be seen in that the SNAP trial reported only 14 pregnancies which did not end in a live birth, due to miscarriage and still birth. However, ESIP suggests that there were 111 pregnancies lost. Furthermore, ESIP uses the risk of foetal loss (ectopic and miscarriage) from population estimates to calculate the number of mothers who experience these adverse events. These risks may be slightly different to the included women in the SNAP trial as they may include specific differences in characteristics compared to the population as a whole. Therefore, it is to be expected that there is going to be a difference in the number of foetal loss events between the SNAP and ESIP estimates.

Furthermore, there appear to be differences in the number of reported adverse events in the trial and the number estimated by ESIP. This may cause ESIP to overestimate healthcare costs associated with within-pregnancy and potentially overinflate the possible healthcare cost savings generated by the SNAP intervention, which may lead to an ICER which suggests that the SNAP intervention offers more value for money than it does in reality. However, conducting a PSA aims to mitigate this issue by providing a summary measure of the level of confidence that the ICER generated by ESIP is the correct value.

10.5.2 Strengths of this analysis

The main strength of using ESIP for the SNAP intervention is that it has now been possible to fit QALY data to the increased quit rate generated by the intervention, giving some idea

of the benefits potentially gained both at the end of pregnancy and across the lifetime of the mother and childhood of the infant. This means that the SNAP intervention can now be compared with other healthcare interventions currently being utilised by the NHS, as the estimates for the ICER per QALY gives a generic summary measure, allowing comparability. Furthermore, whereas the SNAP trial was only able to follow up participants for up to two years after pregnancy, ESIP has extended the time horizon up to the age of 100 for the mother and age 15 years for the infant, giving long term estimates for the potential health benefits of the SNAP intervention. These estimates would be almost impossible to collect using trial data and hence using the ESIP model could be considered the next best approach.

10.5.3 Comparison of SNAP trial and ESIP results

The SNAP trial estimated that there was a £91 increase in expected costs in the experimental group compared to controls, with an ICER of £4,156 per additional quitter (95% CI -£65,994 to £82,059). These included both healthcare costs associated with the mother and those associated with the infant at the end of pregnancy. For the deterministic analysis ESIP estimated that the incremental cost per quitter was £2,932.10, with an increase in expected costs for the experimental group of £52.79. If we assume that the SNAP estimates are the gold standard for estimates for costs and cost-effectiveness of NRT within-pregnancy, then this suggests that ESIP is underestimating the expected increase in costs between the two groups and hence this may explain why the ICER per quitter as determined by ESIP was smaller. However, the difference between the within-trial estimates and those generated in the deterministic analysis is small and therefore it could be considered that ESIP is producing valid within-pregnancy results. The probabilistic results were relatively similar, with a mean incremental cost of £53.27 per pregnancy. However, ESIP suggested that there was a relatively wide 95% CI, which stretched from -£20.93 to £141.57, which the within-trial estimates also lie within. The ICER per quitter under the probabilistic analysis was slightly less, estimated to be £3,001.14, with a narrower 95% CI than that generated by the trial (95% CI -£19,360.13 to 25,094.05). Both the mean ICER per quitter and its associated CI generated by ESIP lie within the 95% CI as found by the within-trial analysis, and therefore it would seem sensible to assume that ESIP

is producing comparable results to that found in the SNAP trial and hence the estimated ICERs per QALYs and other outcomes generated by ESIP could be deemed valid.

10.5.4 What policy makers can take from this analysis

If the policy maker is only interested in within-pregnancy outcomes associated with the mother, both the deterministic and probabilistic results suggest that the SNAP intervention does not offer value for money, assuming that the maximum willingness to pay per incremental QALY is £30,000. [36] The results also suggest that the chance of the SNAP intervention being cost-effective is 0.2813 at that willingness to pay, which suggests that lack of confidence that the SNAP intervention is cost-effective within this time horizon. However, the policy maker may wish to know that even if they weren't willing to pay for any health benefits, there is an approximately 9% chance that the SNAP intervention will offer healthcare cost savings. However, the CIs associated with the ICERs per QALY are extremely large at the end of pregnancy, which suggests a great deal of uncertainty associated with these estimates. The decision maker would probably be sensible to request a value of information (VOI) analysis to determine where best to focus further resources to reduce this uncertainty; however, the deterministic one-way sensitivity analyses potentially suggest that some of this uncertainty is likely to be associated with the cost of the experimental and control group interventions rather than its effectiveness.

Should the policy maker be interested in the lifetime perspective for the mother, both the deterministic and probabilistic results suggest that the SNAP intervention offers value for money, with mean estimated ICERs per QALY which are well within the assumed threshold of £30,000 per incremental QALY. Furthermore, the PSA suggests that there is greater confidence that the SNAP intervention offers value for money at that willingness to pay, with an estimated probability of being cost-effective of 0.5933. However, there is still a large degree of uncertainty associated with the ICER per QALY, and therefore it would seem pertinent to perform a VOI analysis. However, it would seem most likely, based on the results of the one-way sensitivity analyses, that the VOI is likely to suggest that further information is required around the costs associated with the experimental and control interventions. Furthermore, the policy maker may wish to be aware that if they are not

willing to pay for any health benefit, there is now an approximately 15% chance that the SNAP intervention offers healthcare cost savings. However, there is also an approximately 35% chance that the intervention offers no health benefits for the mother across her lifetime.

If the policy maker is interested in including outcomes associated with the infant, there is weak evidence to suggest that, both at the end of pregnancy and age up to 15 years, the SNAP intervention offers healthcare cost savings, as well as reducing some adverse birth outcomes and childhood morbidity. Both the deterministic and probabilistic results suggest that, considering just within- pregnancy, the SNAP intervention is not cost-effective, with a 30% chance of being cost-effective at the assumed willingness to pay of £30,000 per QALY. When extending the time horizon to include the childhood of the infant, the SNAP intervention now becomes dominant, with a 65% chance of being cost-effective. Additionally, even if the policy maker was not willing to pay for any health benefit there is an approximately 10% chance that the SNAP interventions offers healthcare cost savings by the end of pregnancy, increasing to approximately 15% when considering the lifetime and childhood time horizons. However, there is still a 30% chance that the SNAP intervention won't offer any health benefits for either the mother or the infant, or both. There is still a high degree of uncertainty associated with our ICER estimates, which may require additional exploration.

10.6 **Summary**

This chapter demonstrates how ESIP can be used to evaluate a cessation intervention which was conducted as part of a clinical trial. In this scenario, ESIP suggests that from a within-pregnancy time horizon, the SNAP intervention is not cost-effective; however this decision is reversed when the longer time horizon, including lifetime and childhood for the mother and infant respectively, is included. ESIP also suggests that there is a small chance that the SNAP intervention will offer healthcare cost savings, but there is an even greater chance that it will offer no additional health benefit to the mother, her infant, or both. This chapter also provides some reassurance that ESIP produces results which, compared to the within-trial analysis conducted as part of the SNAP trial have some validity; it would appear

that ESIP produces similar estimates for the cost-effectiveness of the SNAP intervention and that in both cases the CIs between the within-trial and ESIP estimates overlap, which suggests there was no significant difference between the within-trial and model estimates. We can therefore conclude that ESIP is likely to be a valid model for estimating the cost-effectiveness of cessation interventions in pregnancy.

Chapter 11: Conclusions of this thesis

11.1 Introduction

This chapter summarises the work conducted throughout this thesis. In it, the author will highlight the limitations of the thesis work, its strengths and also its impact on the current literature. Finally, the author will discuss the possible impacts of ESIP in terms of policy, and suggests what future avenues of research may be appropriate.

11.2 The thesis in context of its aims and objectives

This thesis set out to develop a new economic model that would capture the impacts of smoking during pregnancy on the costs and health related quality of life of both the mother and her infant. The outcome is a complex economic model, which investigates the impacts of smoking on within-pregnancy complications and post-pregnancy smoking behaviour on the health of the mother and the infant. The steps that the author has taken to complete the main objective are as follows:

1. A comprehensive scoping review, which identified the most relevant diseases associated with smoking during pregnancy.
2. A systematic review of the previous economic literature highlighting the important deficiencies of those models, allowing the authors to focus on which aspects needed the most improvement
3. A systematic review of abstinence in the postpartum period in order to better capture maternal smoking behaviour after pregnancy
4. Four standalone models, referred to as 'components', which model the short- and long-term aspects of smoking during pregnancy associated with both the mother and the infant

To the author's knowledge, no such comprehensive and systematic approach has been applied in this topic area before. This has led to a systematically developed new economic

model for cessation interventions within-pregnancy, and as such the author feels he has met the aims and objectives that he initially set out to undertake. The comprehensive scoping review of conditions (Chapter 2) systematically identified morbidities causally associated with smoking, thus meeting objective one. The author has critically assessed previous economic evaluations of cessation within-pregnancy, as detailed in Chapter 3, and thus meets objective two. Furthermore, the author has estimated the best estimates given the lack of available data for postpartum relapse utilised in ESIP, hence meeting objective three. How these estimates are generated is discussed in Chapter 4. Objectives four and five are met in Chapter 5 where the MWPC and IWPC components are described, which capture the influence of the mother's smoking behaviour not only on her health but also on the health of her infant, with a direct link between the two models. In Chapter 6, the author describes the structure of the MLC, which captures the smoking behaviour of the mother post-pregnancy for her remaining lifetime, thus meeting objective six. Chapter 7 describes the structure of the ICC, a model which links the mother's smoking behaviour in the MLC and MWPC with the health of her infant, controlling for passive smoking and birth outcomes for the infant; hence the author feels that the thesis also meets objective seven. Finally, objective eight is met in Chapter 8 as the author describes how the four components of the final model, the MWPC, IWPC, MLC, and ICC, were combined into one model (ESIP), which can be utilised to evaluate within-pregnancy interventions, and how the model was constructed in Excel. Furthermore, the author has gone beyond the specified objectives by demonstrating how the deterministic model was adjusted to allow a PSA to be conducted (see section 8.5), as well demonstrating the how the ESIP model can be used to evaluate one such smoking cessation intervention (see Chapter 10). Therefore, it can be concluded that the aims and objectives set out at the start of this thesis have been met.

11.3 **Brief summary of the chapters in this thesis.**

This section briefly describes the content and main findings of each chapter.

Chapter 2 describes a structured scoping review which was carried out to identify relevant conditions to be included in the economic model, as well as the incidence and utility

decrements/weights associated with these diseases. The review identified that smoking in pregnancy was causally associated with ectopic pregnancy, miscarriage, placenta abruption, placenta previa, pre-eclampsia, preterm premature rupture of the membranes (PPROM), premature birth, low birth weight, Sudden Infant Death Syndrome (SIDS), and childhood respiratory illnesses.

Chapter 3 describes how the author performed a systematic review of previous economic evaluations to critically assess the previous literature and identify methodological issues which might be important for the improved economic model. Quality assessment of included studies was performed using the QHES checklist, and this identified that, out of 18 included studies, only six could be considered high quality. The limitations of the literature identified were that few studies used health related quality of life as the primary outcome; most were focused on a within-pregnancy time horizon, with lifetime impacts excluded in all but four models; no studies included all the diseases the author identified in chapter 2; postpartum relapse was explored haphazardly; and only four studies used statistically robust techniques to control for uncertainty. These were identified as the major issues that a new improved economic model needed to address.

Chapter 4 outlined another systematic review, completed to produce estimates of abstinence in the postpartum period. Focusing on studies of within-pregnancy interventions identified from two Cochrane systematic reviews [27, 28], 26 trials were included in the review. Data on postpartum abstinence was available for up to two years post-pregnancy; however, biochemically validated abstinence was only available for up to six months postpartum. The review estimated that abstinence was 13% at the end of pregnancy, 7% at one year postpartum, and 5% at two years postpartum. The author found no significant difference in postpartum abstinence between control and intervention groups, and no significant difference in abstinence when using biochemically validated evidence only.

Chapter 5 outlines the two within-pregnancy components of ESIP, the MWPC and IWPC. The two models were decision trees with linked parameters, allowing for a direct link between the mother's smoking behaviour and risk of a complication to impact on the

health of the infant. Healthcare costs were calculated from NHS reference costs [298] in 2011/12 prices. Utility values for smokers and quitters were taken from Maheswaran et al [295], with a utility loss associated with ectopic pregnancy and foetal loss. No utility values were placed on infants, but rather the measures of cost-effectiveness for the IWPC were the number of adverse live births (low birth weight and/or premature birth) avoided and adverse birth outcomes avoided.

Chapter 6 describes the mother's lifetime component of ESIP, which is a Markov cohort simulation with five states modelling the mother's smoking behaviour post-pregnancy. The MLC includes four co-morbidities: Coronary Heart Disease, Chronic Obstructive Pulmonary Disorder, Lung Cancer, and Stroke. The number of women with these diseases are calculated in each cycle and costs are applied using 2011/12 prices and discounted at 3.5%. Utility values come from Maheswaran et al for healthy smokers/ quitters [295], while other literature sources are used for the utility values associated with co-morbidities (see Table 6.11), calculating QALYs in each cycle, which are also discounted at 3.5%.

Chapter 7 outlines the infant childhood component, which links the mother's smoking behaviour both within-pregnancy and postpartum with the health of the infant and its exposure to passive smoking, up to the age of 15 years. The ICC is a Markov model with seven states representing the mother's smoking behaviour in the MLC, and as such shares parameters with the MLC. The ICC also controls for the increased mortality associated with LBW. Childhood asthma is the co-morbidity included in the ICC, controlling for within-pregnancy smoking behaviour, passive smoking exposure, and birth weight, with the number of infants suffering from asthma estimated in each cycle. Healthcare costs associated with asthma as well as a 0.1 utility decrement are applied, and all costs and benefits are discounted at 3.5%.

Chapter 8 describes how the four components were brought together into the ESIP model, defining the influence link where the mother's smoking behaviour influences on the child's health, and the flow link which is the sequential nature of the ESIP components. Furthermore, the chapter describes how ESIP was parameterised to perform a probabilistic sensitivity analysis.

Chapter 9 demonstrates a validity exercise for the within-pregnancy components of ESIP compared to population values. The population estimates used in parameterising the MWPC and IWPC were bootstrapped 10,000 times to produce reasonable estimates for the confidence intervals and distributions for these parameters. ESIP was then programmed to perform a PSA to replicate the population values, using 10,000 Monte Carlo simulations. The MWPC was identified to produce valid results for within-pregnancy foetal loss, within-pregnancy complications, and maternal death. Conversely, the IWPC was found to produce much lower mean estimates for infant birth outcomes, with distributions that were wider than the bootstrapped population estimates, which suggest that the IWPC is potentially invalid and its results should be treated with caution.

Chapter 10 displays how the ESIP model can be programmed to perform an evaluation of a cessation intervention. Data from the SNAP trial evaluating NRT against placebo patches was programmed into ESIP [123], and the results of the deterministic and probabilistic analyses were displayed. Although the SNAP trial only produced an estimate of the incremental cost per quitter at the end of pregnancy, ESIP was demonstrated to produce valid results. When combining costs and outcomes for the mother and infant, ESIP estimated that the incremental cost per QALY at the end of pregnancy was £1,123.52 (95% CI -£649,654.26 - £463,317.24), but was dominant when considering the lifetime/childhood perspective. The probability of cost-effectiveness at a willingness to pay of £30,000 per QALY at the end of pregnancy was 0.54 and was 0.65 when considering the lifetime/ childhood perspective.

11.4 Limitations related to the chapters on the development of the model

This section briefly outlines the limitations associated with the first three chapters of this thesis, and discusses their impact.

There are several limitations associated with the scoping review in Chapter 2, which can be summarised as follows:

- There was no quality assessment performed on included studies, and therefore it is impossible to tell whether the review results are based on high quality studies.
- The search was limited to only a few search terms and one electronic database.
- There has been no exploration of the impact of publication bias.

Although these concerns have been highlighted, it is important to consider that performing a systematic narrative review on the amount of literature covered would have been impossible within the confines of this thesis. The review is comprehensive in that it covers evidence relating to 32 conditions, and appraises approximately 4,000 citations, making it, to the author's knowledge, the most comprehensive review of evidence of conditions relating to smoking in pregnancy to date. Furthermore, although the included studies were not formally assessed, a recognised standard for determining if smoking has a causal relationship was used, by particularly focusing on what is considered the gold standard of evidence; systematic review.

The limitations for Chapter 3 revolve around the use of the QHES checklist as the quality assessment of included studies; namely that it is a subjective instrument, the scoring system is inflexible when only part of a question requirement is met, that the QHES itself could lead to potential bias and exclude high quality information, and finally that the additional specifications introduced to the QHES around statistically robust controls for uncertainty, inclusion of all the conditions identified in Chapter 2, and a time horizon covering both within-pregnancy and the lifetime of the mother, may also introduce bias in favour of this piece of work. However, it could be argued that this use of the QHES has allowed a systematic demonstration of the methodological shortcomings of the previous literature. Although the QHES scores are reported, the actual results of interest are the responses to the individual questions, as it is these which highlight the limitations in the previous literature of smoking cessation within-pregnancy. Furthermore, the broad search strategy utilised by the review has probably identified all the relevant studies in this topic area, making it the most comprehensive review to date.

For the review conducted in Chapter 4, the limitations identified were:

- The review estimated patterns of abstinence rather than relapse curves, due to the lack of longitudinal data available, and hence it may be underestimating relapse;
- Not all included studies reported data at all time points, and consequently several time points had very few studies to combine;
- The primary and secondary analyses used both self-reported and biochemically validated abstinence, with self-reported abstinence only beyond six months postpartum, hence there may be some reporting bias inflating the abstinence at those time points;
- Heterogeneity was high at most time points, suggesting that studies should not have been pooled together;
- There was evidence of publication bias, with small studies appearing to be absent from the included studies.

To counter this, it should be noted that point abstinence has been demonstrated to capture 74% of relapse, [362] and that therefore the review is not underestimating relapse significantly. Furthermore, there was a complete lack of longitudinal data, which made it impossible to determine any relapse estimates in the postpartum period. Although the review included self-reported abstinence, when performing a sensitivity analysis controlling for biochemically validated abstinence, the author found no statistically significant evidence of difference in abstinence between the analyses that included self-reported data and those that didn't. Additionally, it was expected that heterogeneity would be high, as there is a great variety of cessation interventions included, but there are not enough studies to break the interventions down into separate categories; this may be possible in the future. Finally, it should be highlighted that all the included studies were trials, and as such could be thought of as the gold-standard in data quality. While other observational and cohort studies may be have been able to provide longer estimates of postpartum smoking behaviour, the quality of the data collected is likely to be lower, and hence would not add anything to the review.

11.5 Limitations of individual model components

As has been mentioned, ESIP is formed of four components into a complex overall model. However, as each model can be considered an individual model in its own right, they each have their own individual limitations. What follows is a brief summary of the limitations for each component.

11.5.1 Limitations with the MWPC

A more detailed discussion of the limitations with the MWPC is given in Chapter 5; however they can be summarised as follows:

- Are the risks of a quitting smoker the same as a never smoker? If this assumption is incorrect, then both the MWPC and IWPC will be overestimating the benefits of cessation since it will be reducing the risks of within-pregnancy complications and adverse birth outcomes too much for women who quit smoking in pregnancy. This would suggest the ICER estimates of the MWPC are too low.
- Does the timing of cessation affect the risk of complications? The MWPC assumes that women who report being quit by the end of pregnancy have the same risks of within-pregnancy complications and foetal loss as women who were never smokers, irrespective of whether they quit early in pregnancy or just before they give birth. Similarly, women who report smoking at the end of pregnancy have been assumed to have smoked throughout pregnancy, even though they may have quit and relapsed just before birth. This suggests that the MWPC could be either over estimating the benefits from smoking if the former exists, or underestimating the benefits if the latter; however, the size of this potential problem is undetermined.
- The costs associated with pregnancy, particularly with those estimated for a normal birth, may be incorrect. This is because what is considered a 'normal birth' is not defined, and pregnancy can have many complications at delivery which affect how healthcare is delivered, e.g. a woman could have a perfectly healthy pregnancy but an extremely complicated birth. The potentially incorrect costs suggest that the

expected cost estimates generated by the MWPC are incorrect, however the author is unsure what impact this has on the ICER's generated by the MWPC, as it is dependent on whether the MWPC is under- or over estimating the costs associated with pregnancy.

- The utility decrements used, generated by Maheswaran et al are only relevant to the population of England [295], and when compared to UK population Norms [306], they may be overestimating the utility associated with a non-smoking woman, thus suggesting the IWPC is over estimating the benefits associated with cessation within-pregnancy, and consequently the ICERs estimated could be too low.
- No utility loss associated with within-pregnancy complications is applied. This was because the author was unable to identify suitable information for parameterisation. Their omission suggests that the MWPC could be underestimating the benefits of cessation, and thus the ICERs could be too high.
- No utility loss associated with pregnancy was included, and hence we assume that a pregnant woman has the same utility as a non-pregnant woman. If a pregnant woman has a lower utility compared to a non-pregnant woman, then the MWPC may be overestimating the total utility at the end of pregnancy; however, it should not make a difference to the incremental difference in benefits at the end of pregnancy, as the utility loss associated with pregnancy would be applied to both groups, and thus should have no impact on the overall cost-effectiveness estimates.
- The MWPC does not include PPROM, which was identified as having a causal association with smoking during pregnancy, due to being unable to differentiate the effect of smoking within-pregnancy on PPROM and PROM, the latter showing no link with smoking during pregnancy. Furthermore, PPROM is closely linked with premature birth, so it would have likewise have been difficult to distinguish the two.

11.5.1.1 What are the potential implications of these limitations?

Although there is a concern with regard to the assumption that quitting smokers have the same chance of an adverse pregnancy event as never smokers, and also the assumption

regarding timing of cessation, the validity exercise performed in Chapter 9 should be considered. This chapter demonstrated that the MWPC produced slightly conservative, but very close, estimates for the number of ectopic pregnancies, miscarriages, placental abruptions, placenta previa, pre-eclampsia, and maternal death compared to population estimates. This would suggest that despite these shortcomings, the MWPC is still estimating the correct number of complications, and is therefore correctly specified and valid. Although there may be slightly conservative estimates of complications, the MWPC is likely to be therefore producing conservative estimates for the cost-effectiveness of the interventions, and therefore erring on the side of caution. Such conservative estimates are only likely to be an issue if the intervention is on the borderline of cost-effectiveness.

With regards to the limitations of within-pregnancy costs, this could be a tricky issue, as it could be argued that the MWPC is inaccurately measuring the healthcare costs associated with pregnancy. However, the author has attempted a fairly detailed and systematic approach to the healthcare costs within-pregnancy, including consulting with a practising midwife to determine the most appropriate approach to attributing costs. Therefore, it is hoped that the model allayed this issue.

The author does not believe the lack of a pregnancy specific utility for women or the lack of utility losses associated with within-pregnancy complications to be an issue. This is because: 1) a utility decrement associated with pregnancy itself would not impact on the results of the incremental analysis as all women in the cohort would have this value applied, and 2) as Chapter 2 highlighted, there was no evidence that any of these within-pregnancy complications had an impact on the quality of life.

Conversely, the utility values and decrements used from Maheswaran et al could prove to be of a concern, since they limit the generalisability of the MWPC to the English population only. [295] While this could be an issue for ESIP in its current state, the model in question is a flexible model, which allows for easy changes in parameterisation. Therefore, if future researchers/ policy makers from other countries/populations wish to use the model, it is simply a case of modifying the utility values to suit their population, and ESIP will produce valid results for them.

Finally, the omission of PPROM could also be a concern for the model. However, as discussed in Chapter 5, in most cases of PPROM/PROM the pregnancy results in a normal birth, suggesting that there is no additional healthcare costs, or that these additional costs are insignificant. Furthermore, in Chapter 2 the author found no evidence that these conditions had any impact on the mother's quality of life. Therefore, it is unlikely that their omission will have any impact on the cost-effectiveness estimates generated by the MWPC.

11.5.2 Limitations of the IWPC

There are several limitations associated with the IWPC as highlighted in Chapters 5 and 9. These can be summarised as follows.

- The IWPC does not include congenital anomalies and the associated costs and health impacts on the infant. Therefore, the IWPC could be underestimating the total healthcare costs for an infant, and the associated cost-savings generated by cessation, not to mention the health and quality of life gains to be had from preventing a congenital anomaly associated with smoking within-pregnancy. This would suggest that the ICER estimates generated by the IWPC are too high, underestimating the value for money of cessation interventions.
- As highlighted in Chapter 9, the IWPC does not seem to produce close estimates of the number adverse birth outcomes, such as stillbirth, low birth weight, and premature birth. In all cases there appeared to be a large difference between the IWPC estimates and the population estimates, with the IWPC consistently underestimating the number of events. Furthermore, the distributions produced by the IWPC were much wider than those population estimates, suggesting that this issue with the IWPC is introducing a greater amount of decision uncertainty into the evaluation.

11.5.2.1 What are the potential implications of these limitations?

Although the IWPC does not include congenital anomalies, the author does not think that this is an issue. As highlighted in Chapter 2, congenital anomalies are relatively rare, and very variable, with the high healthcare costs and high impacts of quality of life only really associated with those conditions which are very severe, which are even rarer. Therefore, if these conditions had been included, by the time the IWPC had taken them into account, the overall expected cost for these conditions would have been very low, and therefore would have had very little impact on the total healthcare costs calculated by the model. Furthermore, the cohort required to generate a change in the number of congenital anomalies averted would have to be exceedingly large, and then it is likely that cessation may only prevent one congenital anomaly. However, it would probably prevent hundreds of low birth weight infants, with which the majority of costs are associated.

As discussed in Chapter 9, it is unclear how significant the concerns around validity of the IWPC are. The author suspects that the cause of the wide differences in the means between the IWPC output and the population estimates is the difference in the rates of premature birth in the HES data (which was based on one year), which are lower than the ONS estimates; this in turn impacts on the risk of LBW and stillbirth. Unfortunately, this cannot be addressed presently as the author does not have the available data, and therefore the estimates of the IWPC must be treated with caution until additional data is available.

11.5.3 Limitations of the MLC

A detailed discussion regarding the limitations associated with the MLC is given in Chapter 6, however they can be summarised as follows:

- There is no inclusion of subsequent pregnancies, which may impact smoking behaviour. This would suggest that the MLC might not accurately capture the smoking behaviour post-pregnancy, suggesting that the ICER estimates are too high, as more women should be estimated to have quit in later cycles.
- Myocardial infarction is omitted from the MLC, unlike previous models [129, 139], and therefore the MLC is underestimating the benefits from smoking cessation and consequently the ICERs may be too high.

- The postpartum abstinence probabilities are based on self-reported abstinence and not from longitudinal continuous abstinence data. It may be that relapse is higher, and this is not being captured by the MLC, hence the MLC estimates of the ICER for cessation interventions are too low.
- The MLC allows for numerous quit attempts to be made post pregnancy due to the Markov assumption, which may be considered unrealistic. As discussed in Chapter 6, a woman may only require six or seven quit attempts before she finally succeeds in permanent cessation, but the MLC does not take this into account. Therefore, it could be argued that the MLC is overestimating the number of women who are smoking in later cycles, hence underestimating the benefits of the cessation intervention. This would suggest the ICER estimates generated by the MLC could be too high.
- Related to quit attempts, the MLC includes a small probability for a long term quitter to relapse, which is applied to all cycles of the MLC. As is highlighted in Chapter 6, there is evidence to suggest that once a smoker has been quit for a long period of time, the risk of their relapsing is very small, and hence this assumption is incorrect. This would suggest that the MLC is overestimating the number of women smoking in later cycles, and hence underestimating the benefits of cessation, implying that the ICERs are too high.
- The relative risks associated with the lifetime co-morbidities are from US data and not England/ UK data. Do these values really apply to these conditions in the population modelled by ESIP even though it is parameterised for the English population?

11.5.3.1 What are the potential implications of these limitations?

The author does not think the omission of subsequent pregnancies is a problem. Although any subsequent pregnancies are likely to lead to changes in smoking behaviour, pregnancy is a relatively short time (less than one year), and the mother may have already relapsed, having given up during her subsequent pregnancy. Furthermore, controlling for any subsequent pregnancies would be very difficult for a model to undertake, and would likely lead to a model too complex to construct.

The omission of myocardial infarction is also unlikely to be a concern. While there is significant mortality, healthcare costs, and quality of life issues associated with a heart attack, these are spread over relatively short periods, and hence a woman may regain her health within one cycle of the model. Furthermore, the inclusion of MI may risk double-counting with the effects of CHD, as the two conditions are quite closely linked. Therefore, the author does not believe the omission of MI to be a major concern.

Although the postpartum relapse probabilities are not from longitudinal data or biochemically validated data, it was concluded that this is the best data available regarding postpartum relapse should women have received a smoking cessation intervention within-pregnancy. It has been demonstrated that self-reported data captures 74% of relapse compared to biochemical validated data [362], therefore even if the biochemically-validated data was available, it is unlikely that the relapse rate would be significantly higher. Furthermore, the longitudinal data for postpartum relapse simply does not exist, although this may change in the future. Therefore, the author feels that this is not a major concern, but would like to highlight that the MLC has the flexibility to be adapted in the future should such information become available.

With regards to the assumptions on the number of quit attempts and the long term relapse probability, the author would again argue that these are not major issues. The introduction of the required memory into the Markov to take into account the past smoking history of the mother would be exceedingly difficult, and produce a bushy Markov, as discussed in section 6.10.2. The author does not believe that the added complication such a Markov structure would bring would give much in the way of advantage over the current structure of the MLC. Furthermore, as highlighted in Chapter 6, there is evidence that individuals can relapse to smoking after a long time, and therefore it would seem reasonable to include this assumption. Thus the author does not believe this to be of concern.

The final limitation, of the relative risks for the co-morbidities of the disease coming from US data rather than UK/ England data, is a possible problem. However, both the rates of CHD and COPD have been demonstrated to be similar in the US and the UK [363, 364], suggesting that using the same risks of developing the diseases are appropriate. However,

the rate of stroke in the UK is higher than the US [365], and the rate of lung cancer is higher in the US than the UK [366], so this would suggest that there is potential for the risks to be different in the English population compared to that of the US. However, the MLC is flexible in that should better parameters for the English population should be identified, then these could be programmed in to correct this issue.

11.5.4 Limitations of the ICC

There are several limitations associated with the ICC, as considered in Chapter 7. They can be summarised as follows.

- The ICC does not include passive smoking associated with mother's partner. This can have an impact on the health of the child as well, and this exclusion could mean the ICC is underestimating the benefits of cessation (if the partner quits smoking as well), producing ICERs that are too high.
- The ICC does not include other impacts outside of passive smoking, such as socioeconomic status, which is associated with smoking. As highlighted in Chapter 7, people of lower socioeconomic status tend to have lower quality of life and higher rates of morbidity, but the ICC does not capture this. Smoking cessation could have lower rates of benefit amongst these individuals; hence the estimates of the ICERs generated by the ICC may be too high.
- Only singleton pregnancies are taken into account, with multiple births excluded. The exclusion of multiple births suggests that the ICC is underestimating the benefits from cessation, and therefore the ICER estimates are too high.
- No subsequent births are included, and these subsequent pregnancies are also likely to be affected by the mother's smoking behaviour. This suggests that the ICC may be underestimating the benefits from smoking cessation, and that the ICER estimates are too high.
- Sudden Infant Death Syndrome was excluded. This was identified as causally associated with smoking during pregnancy in Chapter 2, but was excluded from the model. This could suggest that the ICC is underestimating the benefits from smoking cessation and hence the ICER estimates for cessation interventions are too high.

- Only asthma was included in the ICC; other respiratory illnesses were excluded. This could suggest that the ICC is underestimating the benefits from cessation, and that the ICERs are too high.
- No utility loss associated with a LBW infant was applied. If such a utility loss does exist, then the ICC would be underestimating the benefit of cessation within-pregnancy, and hence the ICER estimates would be too high.

11.5.4.1 What are the potential impacts of these limitations?

It is not believed that the exclusion of passive smoking from the mother's partner is an issue. This is because the cessation intervention is given to the smoking mother and not her partner (although the author is aware that interventions for both mother and partner do exist). As such, the only significant consideration is whether the mother's smoking behaviour changes, and what impact this has on the infant. Therefore, the author believes that passive smoking relating to the partner is exogenous to the model.

With regard to other factors outside of passive smoking, such as socioeconomic status of the mother and her child, it should be highlighted that this model was constructed to represent the average mother in England, ensuring it is of most interest to a policy making body such as NICE. However, it would be possible to run a sub-group analysis focusing in on such women and infants, if suitable parameters for the ICC could be derived.

Although the ICC excludes multiple pregnancies, it could be argued that this is not an issue. This is because if an intervention was to be cost-effective for a single infant, then it is likely that it will be cost-effective for multiple infants. Thus the ICC's current estimates could be considered the upper bound of cost-effectiveness.

The author does not believe the exclusion of subsequent births to be an issue. This is because the model focuses on a cessation intervention given to a woman in a specific pregnancy, and therefore only interested in the impact of that cessation intervention on

that one child. Hence, it could be argued that subsequent pregnancies are exogenous to this evaluation. Furthermore, it could be contended that future lives are not improvements in health, and hence should not be included in the model. [145]

Although SIDS has been causally linked with smoking, the author does not believe its exclusion to have significant effect on the outcomes produced by the ICC. As identified in Chapter 2, SIDS is a rare condition. Furthermore, the model already controls for SIDS in the mortality estimates from the ONS, but it cannot put a specific healthcare cost on this. Therefore, the author feels that the omission of SIDS from the ICC does not impact on the cost-effectiveness estimates because it is such a rare condition.

The lack of inclusion of other respiratory illnesses may be a concern for the ICC. However, asthma is one of the most common childhood respiratory diseases, being chronic and with considerable healthcare costs. Other respiratory diseases may be acute attacks, and as such are short lived. The author would argue that the ICC is capturing the most important of the respiratory diseases, along with much of the expected costs associated across childhood. Therefore the omission of other respiratory diseases is not a problem.

As discussed in Chapter 7, although there is evidence that children born with low birth weight may have a lower quality of life, it has also been highlighted that this effect is short lived and only really applies in the first few years of life. [341] While this could be a concern to the ICC, the fact that this only applies to first few years of life, means that its introduction might not have much impact on the overall estimates of the total benefit calculated. Although it is possible that there may still be changes in the incremental analysis due to the benefits gained from avoiding a LBW infant, the flexibility of the ICC means that it would be easy to incorporate such an impact if required.

11.6 Limitations of the overall model

As well as the limitations associated with the separate components, there are several limitations associated with the overall ESIP model, as discussed in Chapter 8. These can be summarised as follows.

- The influence link between the ICC and the MLC implies that in the PSA, the ICC could sample different values to the MLC, because the MLC uses Dirichlet distributions with three categories, while the ICC uses a Dirichelt with four categories. Therefore this may not accurately reflect the mother's smoking behaviour.
- There was no adjustment in the PSA to take into account self-reported values. This is particularly in reference to the postpartum relapse probabilities, which are based on the pooled analysis in Chapter 4; this included self-reported abstinence, which could be biasing the relapse estimates to be lower than in reality. This suggests that the MLC/ICC may be underestimating the number of women who relapse post-pregnancy and the number of infants exposed to passive smoking; therefore ESIP could be overestimating the benefits of within-pregnancy cessation, and hence the ICER estimates may be too low.
- ESIP does not include any lasting health impacts of within-pregnancy complications. If the within-pregnancy complications have a lasting impact beyond pregnancy, then ESIP is currently not capturing these effects on the quality of life of the mother after pregnancy, underestimating the benefits to be gained from cessation, and suggesting that the ICERs may be too high.
- Although ESIP includes the infant's gender in the ICC, the IWPC does not. If there are different rates of adverse birth outcomes for different genders, then this would not be captured within the IWPC.
- The ESIP model uses parameters primarily from the English population, such as the prevalence of smoking within England, and the rates of within-pregnancy complications taken from English hospital episode data. This would suggest that ESIP is only generalizable to the English population, reducing its usefulness internationally.

11.6.1 What are the potential implications of these limitations?

As discussed in Chapter 8, the author has attempted to mitigate for the break in the influence link in the way the Dirichlet distributions are calculated in the ICC, and in theory the approach used means that the ICC sampled parameters will always be slightly smaller than the respective parameter in the MLC. However, the impact of this on the output of ESIP is unclear, as is the extent of any potential bias on the results of the ESIP analysis.

With regards to the lack of adjustment to the PSA and the self-reported data used in determining abstinence values, this is unlikely to be an issue since, as highlighted in Chapter 4, no statistically significant difference between biochemically validated abstinence and self-reported abstinence was found. This would suggest that no adjustment to the PSA to take into account self-reported data was required.

As discussed in Chapter 2 of this thesis, there was no evidence of a lasting impact of within-pregnancy complications. Furthermore, it appeared that one study recommended that pre-eclampsia and other within-pregnancy complications were only acute conditions, and hence any quality of life loss was very short lived and that there were no further impacts on the mother. [157] This would suggest that the author was correct in his assumption to not include these conditions. Chapter 2 also demonstrated that there appeared to be no link between gender and adverse birth outcomes, which further suggests that the lack of gender in the IWPC is not problematic.

As regards to generalisability, this is a practical limitation of the model, since data was readily available for England but not the whole UK, or other countries. This could restrict the usefulness of ESIP internationally. However, the author would suggest that this is a flexible model, which could be applied to any country, although it would require re-parameterisation. However, this is a much simpler and faster task than constructing the model from scratch, and hence it is unlikely that the lack of generalisability is a particular limitation to the usefulness of ESIP.

11.7 **Strengths of ESIP and this thesis**

There are several important strengths concerning the ESIP model and this thesis. These are:

1) To the author's knowledge, ESIP is the first model which has been systematically constructed to specifically model cessation interventions within-pregnancy. When reviewing the previous economic models of smoking cessation within-pregnancy, it was unclear whether the authors of these models had performed such a comprehensive and systematic approach to producing their models, with several evaluations adapting models developed for cessation interventions in non-pregnant populations [139, 196], which may not be correctly specified for estimating the benefits of cessation within-pregnancy.
2) ESIP models a time horizon that covers both within-pregnancy and the lifetime for the mother and up to age 15 years for the infant. The majority of the previous economic evaluations do not include such a time horizon, with only one model including these conditions. [190] Furthermore, ESIP has included many of the within-pregnancy complications, adverse birth outcomes for the infant, and long term co-morbidities associated with the mother and the infant, which few other models have included, with only one study including these conditions. [190]
3) The ESIP model is the first in the within-pregnancy literature which allows the mother's smoking behaviour to directly impact on the health of the infant, both within- and post-pregnancy. No other model has included this link, with one study even stating that it was purposely excluded. [190] This link is a vital component since there are significant healthcare costs and quality of life impacts on the infant from the mother's smoking behaviour.
4) Although a few previous evaluations included a PSA, the number is relatively small: only four did so. Two of these were within-trial analyses [123, 195], while the other two were both models. While Tappin et al fitted distributions to all included parameters [196], Mallender et al only put distributions on the effectiveness and costs associated with the evaluated interventions. [190] ESIP includes a PSA performed on all distributions included in the model, which means it is only the second model in the topic area to do so.
5) The author has demonstrated that ESIP produces valid estimates of the cost-effectiveness of within-pregnancy cessation interventions. In Chapter 9, the author demonstrated that the MWPC produces very similar estimates to the population

ones for within-pregnancy complications and maternal deaths. Furthermore, in Chapter 10, it is proved that ESIP can reproduce a within-trial analysis, estimating comparable within-pregnancy results to within-trial evaluations. Additionally, ESIP can be used to extend the results of the within-trial analyses to estimate the cost-effectiveness of cessation interventions across the lifetime of the mother and the childhood of the infant, which could be very useful for both researchers and policy makers estimating the cost-effectiveness of cessation interventions within-pregnancy.

6) ESIP has a flexible structure, and could be easily parameterised to suit other populations/ countries. This means that in future, policy makers and researchers will have access to an easy-to-adapt model, one that could be considered high quality, meeting standards of good modelling practice, which may not have been true of previous evaluations.

11.8 Who can use ESIP?

ESIP has been developed so that anyone may use the model for evaluating cessation interventions within-pregnancy. For this reason it was developed using a widely available software package, rather than one more specific for economic modelling. In the near future, it is hoped that ESIP will be hosted online on the UK Centre for Tobacco and Alcohol Studies website (see http://www.ukctas.ac.uk/), where researchers, policy makers, and other interested parties will be able to download the model and associated documentation (user guide, evidence of development) to use for their own purposes. It is hoped that by making ESIP widely available, the model will improve the quality of the literature on smoking cessation interventions within-pregnancy.

11.9 What impact will ESIP have on the research community?

It is anticipated that a wide range of researchers, including other health economists, will use the model. It is expected that the majority of researchers interested in ESIP will be those involved with tobacco and smoking cessation research, as these are the most likely to

be involved with evaluating smoking cessation interventions within-pregnancy. However, other researchers may be interested in the structure and programming of ESIP, as it may have relevance to their topic area, especially if they are investigating parental behaviour and its influence on the health of their offspring. One possible future use could be the evaluation of passive smoking interventions, including public health interventions, since the structures of the MLC and ICC lend themselves particularly well to these and could easily be adapted for their evaluation.

Ultimately, the main objective for ESIP in terms of the research community is that through its use, researchers evaluating within-pregnancy cessation interventions will be able to produce high quality economic evaluations which stand up to the scrutiny of the international academic community. Although ESIP in its current form is only generalizable to England, as that is where the parameters have been sought, it is hoped that other researchers will re-parameterise the model to suit their country, and hence ESIP will be a useful tool internationally.

11.10 What impact will ESIP have for policy makers?

ESIP has primarily been designed to meet the criteria as set out by the NICE reference case. [36] As such, the author hopes that ESIP could be utilised to inform NICE policy guidelines on the cost-effectiveness of cessation interventions within-pregnancy. Furthermore, any new within-pregnancy interventions being considered by NICE could be evaluated by ESIP, allowing the policy maker to make easy comparisons between new health technologies compared with those existing. It is hoped that ESIP will improve the decision-making process, allow accurate estimates of the cost-effectiveness of cessation to better inform the policy maker, and thus allow NICE to ration healthcare resources efficiently. Other policy makers from other countries may wish to use ESIP, and certainly its structure would apply to any within-pregnancy cessation intervention anywhere else in the world, given that smoking within-pregnancy has a causal effect on the included co-morbidities. However, policy makers outside of England would have to be careful of the generalisability given the current parameterisation of the model. Despite this, should they have available

data, the author would not hesitate to assist in re-parameterising the model to suit the policy maker's country/ population of interest.

As discussed in section 1.11, it has been highlighted that there is a lack of guidance on whether the benefits associated with the mother and her offspring should be included, with Goldhaber-Fiebert et al suggesting that there needs to be some international consensus. [146] As discussed in section 1.11 and later demonstrated in Chapter 8, the author decided to combine both healthcare costs and benefits for the mother and her offspring. While this may meet current NICE guidance, which is ambiguous on the subject [36], should NICE change this in the future, and no longer wish to include the offspring's costs and QALYs, ESIP is already able to perform a cost-utility analysis for both the mother and the infant separately. This change would likely mean that the policy maker would be interested in a cost-consequence analysis, where the results of the mother and for the infant are presented independently, and ESIP's high degree of flexibility ensures that it would continue to be of benefit in terms of the future decision-making process.

Chapter 10 demonstrates how ESIP can be used to inform policy regarding cessation interventions within-pregnancy. The SNAP trial included an economic evaluation of the SNAP intervention, but only reported an incremental cost per quitter, since the EQ-5D data did not demonstrate any difference between the two groups, which could suggest to the policy maker that the SNAP intervention is dominated by usual care. However, by using ESIP, it was possible to demonstrate that, in reality, the SNAP intervention could be cost-effective, especially when considering costs and benefits for not only the mother across her lifetime, but the infant and its childhood as well. This would suggest that by using ESIP, the policy maker could have prevented an incorrect decision being made with regards to the SNAP intervention. However, the results highlighted that there was a great degree of uncertainty in the analysis, which could be very important to the policy maker, who may conclude that the SNAP intervention requires more research to determine its true cost-effectiveness.

ESIP is already starting to inform public health policy. Recently, contact was made by Public Health England to request the author to estimate the potential cost-savings that could be

achieved for the 22 Clinical Commissioning Groups (CCGs) in the West Midlands of the UK. The author provided estimates of cost-savings that could be achieved by reducing smoking by 1%, 2.5%, 5%, and completely, for each individual CCG, controlling for their prevalence of smoking at delivery. Therefore, it is hoped that this demonstrates the potential usefulness that ESIP has for policy makers.

11.11 Future work and extensions to ESIP

A possible improvement is the improvement of estimates related to the healthcare costs of childhood associated with smoking. Petrou et al have demonstrated that infants born to smokers experience higher healthcare costs and more hospitalisations during the first five years of life. [142] The author is currently working with a research team to put together a research application to gain access to two large databases, The Clinical Practice Research Datalink and Hospital Episode Statistics, [272, 367] in order to extract data relating to women who report smoking and abstinence during pregnancy and the healthcare costs associated with their infants up to the age of 15. Once these values have been generated, the aim is to build these costs into the ICC. This would allow ESIP to calculate better estimates of the healthcare cost-savings generated by cessation. This is something that ESIP does not currently do, except for the healthcare costs associated with asthma.

Another future extension is to construct a further component to represent the health of the child beyond the age of 15. Chapter 7 suggested some evidence that the infant's smoking behaviour is directly influenced by the mother's smoking behaviour during childhood, with the risk of the child becoming a smoker by age 16 doubling if the mother smokes during his or her childhood. [25] Since maternal postpartum smoking behaviour can be somewhat influenced by their smoking behaviour during pregnancy, this implies that the child's smoking behaviour is potentially consequential of smoking during pregnancy. Therefore, by persuading mothers to stop smoking during pregnancy and maintain that abstinence, the intervention may potentially prevent their child from becoming a smoker, saving the NHS money in terms of related healthcare costs attributable to smoking, as well as any health lost by the child. The omission of this 'offspring adult component' (OAC) suggests that ESIP is not capturing the healthcare costs and health losses attributed to this

particular problem, intimating that ESIP is conservatively estimating the differences in costs saved and health gains attributed to smoking related diseases for the child, and consequently the cost-effectiveness of interventions. Although the OAC is beyond the scope of this thesis, the user should be aware of this exclusion.

The ESIP model also omits a value of information (VOI) analysis. A VOI analysis is a tool which focuses on the likelihood of making a wrong decision if a technology is adopted, and calculates the value of additional research based on the extent to which further information will reduce decision uncertainty. [39, 368] This allows a comparison between the costs of further research and the potential benefits of that information, which can be useful for prioritising future research recommendations. [368] A VOI analysis is performed by calculating the expected value of perfect information (EVPI), defined as the expected costs of uncertainty, since perfect information can eliminate the possibility of making the wrong decision. [368] To demonstrate, assume there are uncertainties in an evaluation, defined as θ, and two interventions, t=1,2. It can be assumed that the maximum net monetary benefit can be defined as $max_t E_\theta B(t,\theta)$ from the optimal decision under existing evidence. Under perfect information, the decision maker would know what values θ would take, and hence the expected net monetary benefit with perfect information can be defined as $max_t B(t,\theta)$.

However, since the true values of θ are unknown, the expected value of a decision taken with perfect information can be found by averaging the maximum net benefit over the distribution of θ, defined as $E_\theta max_t B(t,\theta)$. [368] Therefore, the EVPI per patient can be defined by taking the difference between the expected value of the decision under perfect information and the decision based on existing evidence:
$E_\theta max_t B(t,\theta) - E_\theta max_t B(t,\theta)$. [368] However, it is very important that the EVPI should be expressed as the total for all patients, as it can be used to demonstrate where future research could be beneficial. A VOI analysis can also work out the benefit of partial perfect information (EVPPI), where decision uncertainty and net monetary benefit is focused around a specific parameter in the model, thus helping to aid prioritisation within the topic area. [39, 368] VOI analyses are now considered as useful tools for prioritising future research, not only in terms of the research community [369], but also in terms of

prioritising research goals within health technology assessment and policy making decisions. [368]

Performing a VOI analysis in ESIP would be useful as it would allow researchers and policy makers to determine whether 1) smoking cessation interventions within-pregnancy are an important area on which to prioritise funding, and 2) there are specific parameters in ESIP (e.g. postpartum relapse rates) which require further research. However, a VOI analysis in ESIP might demonstrate that there is little or no future gain to be had from further research, which would suggest that ESIP is a satisfactory model for performing evaluations of within-pregnancy cessation interventions. A VOI analysis has been performed before in this topic area. Tappin et al demonstrated that for maternal outcomes alone, there appeared to be a need for further information. [196] The authors estimated that further research was potentially worthwhile if it cost less than £3.3 million. This would suggest that including a VOI analysis might be a worthwhile extension.

The structure of the ESIP is not necessarily restricted to smoking in pregnancy. Both the within-pregnancy and the lifetime and childhood components could be used to evaluate the impact of other harming behaviours within-pregnancy. For example, alcohol abuse within-pregnancy has been linked with similar adverse pregnancy events to smoking. [370-372] It is likely that ESIP could easily be adapted to model alcohol interventions within-pregnancy. Another situation where ESIP could be adapted is passive smoking interventions. The links between the MLC and ICC equally apply to interventions within-pregnancy as well as interventions given to mothers post-pregnancy. Therefore, the author speculates that the structures of the MLC and ICC could be used to evaluate passive smoking interventions, including public health interventions. With future policy focusing on these public health interventions, such as the future ban in October 2015 of smoking in cars, the MLC and ICC are likely to be of particular use in the future.

11.12 Practicalities for future similar economic evaluations

While ESIP could be considered the most thorough model of cessation within-pregnancy constructed to date, the author realises that such a model takes a long time to construct (ESIP took four years in a PhD setting), and requires large amounts of computing power. The time it took to construct ESIP may not be acceptable for policy makers who may wish to undertake rapid appraisals; hence they may not wish to fund such work. Undertaking such analyses requires a lot of resources, which were only possible in the PhD setting where the author was able to focus on ESIP for four years. This may not be practical in other settings, where a researcher might not be able to focus on developing a similar evaluation to ESIP or doesn't have the necessary skills in other areas (e.g. systematic reviewing). However, the process could be quicker if the author had been part of a larger team, with other team members undertaking other aspects (e.g. the systematic reviews). Conversely, additional team members would have led to additional expense which may have been unacceptable to the funder/policy maker. One final consideration is that ESIP is computationally intensive, requiring several hours to perform a PSA. While the author has access to a powerful computer, other researchers may not, preventing them from using ESIP. However, this may change as computers become more powerful in the future.

11.13 Concluding thoughts

The key message of this thesis is that previous economic evaluations are too simplistic and do not produce accurate estimates of the cost-effectiveness of smoking cessation interventions within-pregnancy, which could lead to incorrect policy decisions being made. The author has developed, through a systematic process, an improved economic model for performing economic evaluations on these interventions. Although ESIP is far from perfect, it is a far more comprehensive model of this topic area, with a novel approach of including the post-pregnancy mother's smoking behaviour, impacting on the health of the infant. However, to quote George E P Box, "essentially, all models are wrong, but some are useful". [373] It is anticipated that the outcome of this thesis, the ESIP model, can be deemed a "useful" model.

Chapter 12: Appendices

12.1 Search terms used for identifying utility values

Table 12.1 Electronic search terms used for identifying utility values using Medline

Search number	Search term	Citations
1	MESH exp Quality-Adjusted Life Years/	7347
2	MESH exp Placenta Previa/	2252
3	1 **and** 2	1
4	MESH exp Pre-Eclampsia/	23512
5	1 **and** 4	2
6	MESH exp Pregnancy, Ectopic/	12806
7	1 **and** 6	3
8	MESH exp Abruptio Placentae/	1782
9	1 **and** 8	0
10	MESH exp Fetal Membranes, Premature Rupture/	5794
11	1 **and** 10	1
12	MESH exp Premature Birth	6621
13	1 **and** 12	6
14	MESH exp Asthma/ **or** MESH exp Lung Diseases/ **or** MESH exp Respiratory Tract Diseases/ **or** MESH exp Respiratory Tract Infections/	1087726
15	1 **and** 14	484
16	MESH exp Child/	1561198
17	MESH exp Infant/	945317
18	16 **or** 17	2030827
19	15 **and** 18	79
20	MESH exp Mental Disorders/ **or** MESH exp Child Behaviour Disorders/	963312
21	MESH exp Conduct Disorder/	2391
22	MESH exp Attention Deficit Disorder with Hyperactivity/	20459
23	20 **or** 21 **or** 22	963312
24	1 **and** 23	437

25	18 **and** 24	41
26	MESH exp Congenital Abnormalities/	462605
27	MESH exp Limb Deformities, Congenital/	17312
28	26 **or** 27	462605
29	1 **and** 28	40
30	MESH exp Infant, Low Birth Weight/	26706
31	1 **and** 30	18

12.2 Summaries of strength of evidence for smoking related morbidities

Table 12.2 Summary of strength of evidence found from both scoping reviews in Chapter 2

Conditions associated with smoking	Suggested link (Review 1)	Summary of strength of evidence (Review 2)
	Pregnancy specific maternal conditions	
Placenta previa	7 studies reported a strong association. [1, 2, 4, 374-377] Increased risk of between 1.5 and 3 times [375], OR of 1.28 to 7.42 [377] and 1.58. [2] RR between 1.28 and 4.4.[4]	6 case-control studies, 5 cohort studies, and 1 meta-analysis identified a strong association. [2, 378-388]
Placental abruption	7 studies reported a strong association.[1, 2, 4, 374-377] 1.4 to 2.4 fold increase in risk. [375] OR of 1.4 to 4.0 [377] and 1.62. [2] RR of 1.23 to 4.0. [4]	11 cohort, 10 case-control, 1 systematic review, and 1 meta-analysis found a strong association. [2, 379, 380, 383, 388-406]
Placenta accreta	2 studies reported a strong association. [1, 377]	1 case control study reported a strong association. [407]
Pregnancy bleeding of unknown origin	2 studies reported an association. [1, 377]	No evidence.
Preterm Premature	8 studies reported a strong association. [1, 2, 4, 142, 374-377] Between two and three fold increase in risk. [375] OR	7 case-control and 1 meta-analysis identified a strong association [2, 408-414].

rupture of membranes (PPROM)	of 1.7 [2] and 1.7 - 2.25.[377] RR of between 1.6 and 3.0.[4]	
Ectopic pregnancy	7 studies reported a strong association.[2, 4, 142, 374-376, 415] Between 1.5 and 2.5 increase in risk .[375] OR of 1.7 [2] and 54. [376] RR of 2.2 [30] and 1.77-2.0.[4]	8 case-control, 1 cross-sectional, 1 meta-analysis and 1 review identified a strong association. [2, 416-425]
Pregnancy rhinitis	1 study reported an association. OR of 1.7. [426]	1 survey reported an increase in incidence. [427]
Deep vein thrombosis	1 study reported an association. OR of 1.3. [376]	2 case-control studies reported a significant effect. [428, 429]
Stroke	1 study reported an association. OR of 1.7. [376]	No evidence.
Pulmonary embolism	1 study reported an association. OR of 2.5.[376]	No evidence.
Myocardial infarction	1 study reported an association. OR of 4.6.[376]	No evidence.
Influenza	1 study reported an association. OR of 2.9.[376]	No evidence.
Bronchitis	1 study reported an association. OR of 15.2.[376]	No evidence.
Asthma	1 study reported an association. OR of 4.0.[376]	2 case-control and 1 cohort study identified a strong association. [430-432]
Gastro intestinal ulcers	1 study reported an association. OR of 3.7.[376]	No evidence.

Gestational diabetes	1 study reported a protective association. OR of 0.9. [376]	2 Systematic reviews found no association. [433, 434]. Two cohort studies found no association. [435, 436] 1 cohort, 1 cross-sectional, and 1 randomized trial found an association. [437-439]
Pre-eclampsia	7 studies reported a protective effect. [2, 4, 374-377, 415] OR between 0.7 and 0.8 [376], and 0.51.[2] 30-50% reduction in risk.[375]	3 systematic reviews identified a protective effect.[2, 440, 441] 15 cohort studies [388, 442-455] and 8 case-control [456-463] identified a protective effect. 5 studies found no association.[461, 464-467]
Uterine fibroids	1 study reported a protective effect with a RR of 0.7. [415]	No evidence.
Vomiting during pregnancy	1 study reported a protective effect with a RR of 0.6. [415]	1 Cohort study reported no significant effect [468], while one survey identified a reduced risk. [469]
Joint maternal and infant conditions		
Pre-term birth	9 studies reported a strong association. [1, 4, 142, 375-377, 470-472] OR of 7.25 [472]. RR of between 1.1 and 1.7.[4] Risks between 1.5 and 2 times greater and passive smoking increased risk by 23%.[375]	28 cohort studies, 12 case-control, 2 cross-sectional studies, and 5 review articles identified a significant association. [405, 411, 473-518] 5 cohort studies, and 2 case-control found no significant association [372, 519-524]. 1 systematic review identified no association with passive smoking. [525]

Early and late foetal loss	8 studies reported a strong association. [1, 4, 374-377, 415, 470] 10% of stillbirths attributable to smoking.[470]RR of 1.28 [415] and 0.83 to 2.0 [4] for spontaneous abortion. RR of 1.2 to 1.6 for neonatal deaths.[4] Risk of miscarriage increased by 25% and risk of stillbirth by 40%.[375]	1 systematic review [526], 30 cohort, 11 case-control and 12 reviews identified a strong association. [445, 527-579]. 1 review, 6 cohort, and 4 case-control found no significant association.[524, 580-589].
Infant conditions		
Lower quality of life for infant over lifetime.	3 studies reported a tenuous link.[26, 142, 336] Infants born to smoking mothers stayed longer in neonatal intensive care units (NICU) and visited hospital more frequently in the first 2 years of life.[26, 142] Length of stay in NICU increased as dose increased: 6 days for non-smoking mothers; 7 days for mothers who smoked between 1 and 9 cigarettes a day (OR 1.06); 7 days for mothers who smoked 10 to 19 cigarettes a day (OR 1.11); 8 days for mothers smoked 20+ cigarettes a day (OR 1.21). [142]	1 cohort study reported a strong association.[18]
Sudden infant death syndrome (SIDS)	7 studies reported a strong association. [4, 375, 377, 471, 472, 590, 591] 3 studies identified a 2 fold increase in risk. [377, 471, 590] 40% increase in risk.[377] RR of between 1.4 and 8.4.[4],One study identified a link with passive	2 systematic reviews [3, 592], 5 reviews [593-597], 16 cohort [492, 598-612], and 22 case-control studies [613-634] identified a significant association.

	smoking.[375] Estimated 66% of mothers whose infants die reported smoking during pregnancy. [590]	
Low birth weight (LBW) / Small for gestational age / Impaired growth	10 studies reported a strong association with LBW/reduced birth weight. [1, 4, 142, 375, 377, 470-472, 635, 636] Babies born to smokers had a mean birth weight of 3240g+/-566g versus 3516g+/-571g of babies born to non-smokers.[472] Infant's birth weight reduced between 10g and 12g per cigarette a day. [377] 21% to 39% of LBW babies attributable to maternal smoking (OR 1.4 - 3.0). [4] Mothers who passive smoked more likely to have LBW infants. [375] 11 studies reported a fairly strong association with impaired growth and development of the infant.[1, 4, 375, 415, 471, 472, 636-639] 4 studies reported an effect on growth restriction and limb reduction.[1, 4, 415, 471] RR of 2.1 [415], and 2.3 - 2.8. [4]	6 reviews studies, 1 cross-sectional, 36 case-control, and 117 cohort studies found a significant association between smoking and LBW / small for gestation age/decrease in birth weight. [304, 405, 432, 443, 451, 473-475, 478, 483, 484, 492, 494, 497, 501, 504, 509, 515, 516, 518, 520-524, 528, 568, 640-772] One meta-analysis [3] found a significant link, while one systematic review found a link with passive smoking. [525] 6 cohort, 4 case-control, and 1 cross-sectional study found no significant association. [479, 773-782]
Congenital anomalies (limb malformation)	5 studies reported a strong association. [1, 4, 415, 471, 639] RR of 2.1 [415], and 2.3 - 2.8.[4] Greater risk of developing a physical disability after a musculoskeletal injury (RR 1.44 in young adults). [639]	General abnormalities: 2 systematic reviews [783, 784], 6 cohort, 9 case-control and 2 reviews identified a significant association [551, 597, 785-799]; 7 cohort and 2 case –control studies found no association. [800-808] Gastroschisis (intestine formed outside the body): 1 systematic review

[809] , 5 cohort and 5 case control studies identified a link [810-819]; 1 cohort found no association. [820]

Oral clefts: 3 systematic reviews[809, 821, 822], 6 cohort and 16 case-control studies found a significant association [798, 814, 823-842]; 2 cohort and 5 case-control studies found no association. [843-849]

Neural tube defects: 4 case-control studies suggested an increase in risk [850-853]; 2 case-control and 1 cohort found a reduction in risk [840, 854, 855]; 1 case-control and 1 cohort found no association. [856, 857]

Craniosynostosis (malformed skull): 1 systematic review [809], 2 case-control and 1 cohort found evidence of an association [858-860]; 1 case-control found no link. [861]

Eye / retina: 2 cohort and 2 case-control reported an increase in risk. [862-865]

Congenital heart defects: 3 cohort and 8 case-control studies found an association [799, 839, 854, 866-873]; 2 cohort and 1 case-control found no

		association. [874-876] Downs syndrome: 1 systematic review [877] and 1 case-control [878] identified a reduced risk; 1 case-control found an increase in risk [879]; 4 case-control and 2 cohort studies found no association. [875, 880-884] Digit anomalies: 2 cohort and 1 case-control found an increased risk [814, 885, 886]; 1 cohort found no association. [875] Hypospadias (malformation of the penis) / Cryptorchidism (undescended testicle): 4 studies found an increased risk [875, 887-890]; 2 cohort and 3 case-control found no association [891-895]; 1 cohort study reported a decrease in risk. [896] Rectal / digestive: 3 case-control found an increase in risk [897-899]; 1 study found a decrease in risk. [900]
Cognitive development	4 studies found a strong association. [375, 472, 636, 901], Development delay at 24 months (OR 2.36). [636]3 studies suggested that the infant had a lower IQ in adulthood. [375, 472, 901] Increased risk of an IQ of less than 80	1 case-control and 2 cohort found an association.[902-904] 6 cohort found no association. [905-911] 3 reviews found no association. [910, 912, 913]

	[9].[901]	
Respiratory Illness	11 studies reported a strong association. [1, 4, 142, 336, 375, 376, 470, 472, 636, 914, 915] OR 1.72 for lower respiratory tract infection (LRI). [915] Risk of LRI in Children <5 years old was high (OR 2.5), and remained significant with children >5 (RR 1.63).[336] Increased hospitalisation and deaths caused by LRI (OR 2.41).[336] 8 studies identified an increased risk of asthma. [4, 336, 375, 470, 472, 636, 914, 915] OR 1.46[336], and 11.6. [915] RR 1.3-2.0. [4] High risk even at age of 15 years (OR 1.8). [636]	44 cohort, 9 reviews, 7 case-control, 2 cross-sectional, and 1 meta-analysis found a strong association. [216, 598, 916-974] 3 cohort found no association. [975-977]
Behavioural Problems	7 studies determined there was an association. [1, 142, 375, 376, 636, 637, 978] 3 studies suggested link with ADHD [4, 17, 26].[1, 142, 978] 3 times more likely to have a clinical diagnosis of ADHD. [978] More likely to abuse other substances (drugs, alcohol). [1, 376, 978] 2 studies made a link between maternal smoking and criminality. [1, 978]	7 reviews, 15 cross-sectional, 9 case-control 19 cohort, and 16 longitudinal identified a significant association. [637, 638, 901, 979-1041] One systematic review was identified. [1038] The authors concluded there was a link with ADHD; however, the meta-analysis reported no significant associations. 4 reviews, 2 cross-sectional, 2 case-control, 2 cohort, and 3 longitudinal reported no association. [978, 1042-1053]
Fertility	3 studies found evidence of a reduction in male fertility. [1054-1056]	2 cohort and 1 clinical trial reported no significant effect. [1057-1059] 1 cohort reported a small effect. [1060]
Childhood Cancers	3 studies identified an association. [375, 470, 636] RR of 1.11 for childhood cancers and RR of 1.14 for	2 reviews found no association. [1061, 1062] 13 case-control reported no association. [1063-1075] 6 case-control studies reported an association.

	leukaemia.[375]	[1076-1081]
Otitis media (Middle Ear Disease)	3 studies reported an association. [4, 336, 375] RR of 1.0 - 3.0.[4] OR of 1.19.[336]	2 observational studies reported an increase in the relative risk of Otitis Media. [1082, 1083] 1 Observational Study reported no association.[1084]
Obesity	4 studies reported an association. [375, 376, 470, 1085] 3 times more likely.[376]	2 reviews reported a strong association. [1086, 1087] 1 review did not find any association. [1088] 8 Observational studies and 6 Cohort studies reported a strong association.[1089-1100]

12.3 Characteristics of included studies of previous evaluations of cessation interventions during pregnancy.

Table 12.3 Characteristics of included studies: type of study, interventions and comparators, outcomes, and characteristics of costs

Author/ Year	Type of study	Intervention / comparator	Primary / secondary outcomes	Characteristics of cost data
Ayadi 2006 **[201]**	Observational with hypothetical modelling	5As intervention in three different settings; clinical trial, quit line, and rural managed care organisation / assumed baseline quit if 14%	Assumed quit rate of intervention 30% – 70% versus 14%	Intervention micro-costing in different settings; neonatal care costs for infants of mothers who smoke estimated from CDC software (SAMMEC)
Cooper 2014 **[123]**	Within-trial analysis alongside RCT	NRT with behavioural support / placebo patches with behavioural support	Sustained biochemically validated abstinence between quit date and end of pregnancy / Self-reported abstinence at six months and two years after delivery; infant outcomes included stillbirth, miscarriage, birth	Micro-costing of control and intervention groups, including salary, patches and biochemical validation costs; weighted average NHS reference costs used for HRG data; costs

			weight, gestation age at birth; EQ-5D scores at six months postpartum	reported for 2009/10 financial year
Dornelas 2006 **[202]**	Within-trial analysis alongside RCT	90 minute psychotherapy session at clinic followed by bi-monthly telephone calls with mental health counsellor / Standard smoking cessation treatment guidelines	Biochemically validated seven-day point prevalence at end of pregnancy and six months postpartum	Cost of training, counselling time, telephone time, clerical staff
Ershoff 1983 **[204]**	Within-trial analysis alongside non-randomised trial	Two 45 minute nutrition counselling sessions. Eight week program with home-correspondence. Three telephone calls with reinforcement message / Standard prenatal care from two sources – random sample who attended in four months before program and random sample who attended maxi-care in different area	Self-reported abstinence at two months postpartum / Nutrition behaviour; complications during pregnancy (toxaemia, infection, hypertension, weight gain); infant birth weight; Apgar scores; abnormalities	In-patient claim forms, cost of hospital stay, staff salaries, program development, implementation costs, overheads
Ershoff 1990 **[203]**	Within-trial analysis alongside non-randomised trial	Self-help intervention, series of booklets / usual care	Biochemically validated point prevalence at end of pregnancy / birth weight and low birth categories; intra-	Overhead, time, materials, postage, health plans costs from computerized claims

			uterine growth restriction; pre-term birth	system, charges to health plan, charges from hospital based providers
Hueston 1994 **[205]**	Decision analytic model	Hypothetical intervention / hypothetical intervention with assumed level of effectiveness	Intervention quit rate of 3% - 29% at end of pregnancy versus. background quit rate of 6%, 15% and 37% / rates of LBW amongst smokers estimated from national cohort	Costs of healthcare for LBW infants from literature,
Mallender 2013 **[190]**	Decision analytic model	Interventions come from established literature. Situations modelled were: High intensity versus low intensity behavioural support interventions High intensity behavioural support versus usual care Conditional incentives versus non-conditional incentives	QALYs	Costs for interventions taken from literature; literature based costs used for diseases / conditions; costs reported at 2011 prices
Marks 1990 **[68]**	Decision analytic model	Hypothetical smoking cessation programme / normal care with no cessation intervention	LBW and prenatal deaths prevented	Cost of intervention estimated from 2

				previous studies in USD. Short and long-term costs averted taken from 1986 office of technology cost assessment of neonatal intensive care for LBW infants.
Parker 2007 **[206]**	Within-trial alongside observational (one arm of trial)	Telephone calls providing motivational interviewing / those receiving no calls (either because they chose not to or because contact could not be made). All received a quit kit	Biochemically validated abstinence at end of pregnancy and six months postpartum	Costs of calls using unit price of staff and non-staff – personnel and training time
Pollack 2001 **[71]**	Case-control with hypothetical modelling	Hypothetical intervention using an average of reported success rates cessation programs across various settings / no intervention, no spontaneous quitting	Abstinence rates at end of pregnancy / number of SIDs averted	Cost of typical intervention per participant in 1998 USD
Ruger 2008 **[137]**	Within-trial analysis alongside RCT	Three 1 hour home visits using motivational interviewing (MI) and self-help manuals. MI targeted: 1) impact of smoking on mothers, foetuses, and newborns; 2) evaluated smoking behaviour; 3) increasing self-efficacy for smoking cessation; 4)	Abstinence and relapse prevention at six-months postpartum / birth weight; post-delivery status; LYs; QALYs	Intervention costs collected within RCT. From literature: Cost savings for neonatal intensive care, chronic

		setting goals to change smoking; 5) feedback about household nicotine levels / Standard prenatal care: 5-minute intervention outlining the harmful effects of smoking during pregnancy and self-help materials		medical conditions, and acute conditions during the first year of life, cost savings for maternal healthcare (cardiovascular and lung diseases)
Shipp 1992 **[65]**	Decision analytic model	Hypothetical intervention / no cessation program	Abstinence at end of pregnancy / number of LBW, premature births, placental abruptions, haemorrhage, placenta previa, pre-eclampsia cases avoided	Direct medical charges for maternal care at delivery and hospital care for newborns.
Tappin 2014 **[196]**	Within-trial analysis alongside RCT, extended using a decision analytic model [209]	Standard care from NHS pregnancy stop smoking services plus financial incentives of vouchers up to £400 for women who quit and remained abstinent throughout pregnancy / standard care from NHS pregnancy stop smoking services which involves, face-to-face appointments, support phone calls, and NRT for up to 12 weeks	Biochemically validated abstinence at end of pregnancy, QALYs	Micro-costing using resource use data within-trial, healthcare costs of birth weight and smoking related diseases from NHS Scotland reference costs and

				established literature sources
Taylor 2009 **[139]**	Decision analytic model	Interventions identified by Cochrane review: cognitive behaviour strategies; stages of change; feedback; rewards; pharmacotherapies; 'other' interventions / no intervention with spontaneous quit rate	QALYs	Lifetime costs from previously developed model; costs in first five years of life per infant admitted to hospital born to smoking and non-smoking mothers, taken from Oxford Record Linkage study
Thorsen 2004 **[207]**	Within-trial alongside observational study	The 'First Breath' smoking cessation programme / none given	Abstinence rates at end of pregnancy	Costs of: Maternal maternity admissions, inpatient neonatal care and medical costs for first month of life.
Ussher 2014 **[195]**	Within-trial alongside RCT	Intervention to encourage physical activity with behavioural support / standard behavioural support provided by NHS Stop Smoking Services	Biochemically validated abstinence at end of pregnancy	Micro-costing of intervention and control groups, including salaries, physical activity

				equipment, biochemical validation equipment; weighted average NHS reference costs used for HRG data; costs reported for 2012/13 financial year
Windsor 1988 **[208]**	Within-trial alongside RCT	Two intervention groups: Group 1 given standard information and "Freedom From Smoking in 20 Days"; Group 2 given standard information plus “A Pregnant Woman's Self-Help Guide to Quit Smoking". Both groups received "Because You Love Your Baby", and a 10 minute presentation at the first prenatal visit / Control group received a non- focused interaction on smoking and pregnancy of 5 minutes during the first prenatal visit	Abstinence at end of pregnancy	Salary estimates in USD , cost of manuals
Windsor 1993 **[69]**	Within-trial alongside RCT	Three components: Self-help materials with brief counselling support with follow-up letters and a buddy system / Normal care – not defined	Abstinence at end of pregnancy / LBWs avoided	Salaries of staff delivering intervention. Costs for the LBW infant at birth, in first year of

life and long-term costs

Table 12.4: Characteristics of included studies: type of evaluation, comparison, and results

Author/ Year	Type of analysis	Units of comparison	Perspective of analysis / time horizon / discounting (per annum)	Sensitivity analyses	Results
Ayadi 2006 **[201]**	CBA	Neonatal cost savings per quitter	Provider / within-pregnancy / no discounting	Effectiveness (30 to 70%); intervention cost USD 24 to USD 34	Neonatal cost savings of USD 881 per maternal smoker; net savings of up to USD 8 million based on intervention cost of USD 24
Cooper 2014 **[123]**	CEA	Incremental cost per quitter	Societal / within-pregnancy / no discounting	Uncertainty explored by using non-parametric bootstrapping (1000 iterations) on costs and effectiveness; exclusion of multiple births	Mean cost of control £47.75 with a quit rate of 7.6%; mean cost of intervention was £98.31 with a quit rate of 9.4%; ICER £4,926 per quitter (95% CI -£114,128 to £126,747)
Dornelas 2006 **[202]**	CEA	Incremental cost per quitter	Provider (implied) / within-pregnancy and six months postpartum / no discounting	None	Intervention cost USD 56.37 per patient. Incremental quit rate 18.7 (28.3 – 9.6). Incremental cost per quitter USD 298.76
Ershoff 1983 **[204]**	CBA	Benefit-cost ratio	Provider / within-pregnancy and two months postpartum / no	None	Intervention quit rate of 49.1% versus 37.5% of controls; mean birth weight greater in

			discounting		intervention group, 121.34 ounces versus 113.64; hospital treatment cost differential of USD 183 per delivery; intervention cost USD 93 per patient; benefit cost ratio of 2:1
Ershoff 1990 **[203]**	CBA	Benefit-cost ratio	Provider / within-pregnancy / no discounting	None	Intervention quit rate of 22.2% versus 8.6% for and controls; intervention infants weighed average 57g more; intervention cost per delivery USD 1028 versus USD 1074 in controls; cost savings of USD 5,428; total intervention cost of USD 1,939; benefit: cost ratio of 2.8:1
Hueston 1994 **[205]**	CBA	Intervention cost versus neonatal costs averted	Provider (implied) / within-pregnancy / no discounting	Intervention quit rate between 3% and 29%; spontaneous quit rate of 6%, 15% and 37%	Cessation programmes in pregnancy cost effective for preventing LBW births if they cost $80 or less per participant and achieve quit rates of at least 18% with a spontaneous quit rate of 37%
Mallender 2013 **[190]**	CUA	Incremental cost per QALY	Societal (implied) / up to three years after intervention; lifetime for mother and infant / costs and QALYs at 3.5%	Intervention cost and effectiveness varied in PSA analysis (1000 iterations)	High vs low intensity behavioural: Short term (three years): £5,445, £1,331 Lifetime (mother): £563, £136 Lifetime (mother and infant): £183, £51

					High intensity behavioural vs usual care: Short term (three years): £17,827, £157,696, £2,344 Lifetime (mother): £1,864, £16,515, £244 Lifetime (mother and infant): £528, £4,594, £72 Conditional incentives vs non conditional: Short term (three years): £41,088, £60,409, £43,161 Lifetime (mother): £4,331, £6,441, £4,589 Lifetime (mother and infant): £1,124, £1,488, £1,091 Note: Also ICERs including productivity estimates, not reproduced here
Marks 1990 **[68]**	CBA	Cost per LBW averted; cost per prenatal death averted; benefit-cost	Provider (implied) / lifetime / cost of LBW at 4%	Cessation rates from 5% through to 25%; costs programmes varied USD 5-100; percentage of LBW	Cost per LBW birth prevented USD 4000; cost per prenatal death prevented USD 695,452; costs averted in terms of short term hospitalization USD 3.31 for every USD 1 spent on cessation; long-term costs averted USD 3.26

		ratios for short and long-term hospitalisation costs		needing neonatal special care 33%-67%; relative risk of LBW 1.5 – 2.5; relative risk of prenatal death 1.1 to 1.4	per every USD 1 cessation
Parker 2007 **[206]**	CEA	Cost per quitter	Provider / within-pregnancy / no discounting	Varied costs of intervention per patient from USD 20 to USD 30	Quit rate for no calls 9.6% and 3 calls 23%; effectiveness to cost ratio of 1: USD 84 based on 3 calls
Pollack 2001 **[71]**	CEA	Cost per SIDS averted	Provider (implied) / within-pregnancy / 5% per cost of life year	None	Assumed quit rate of 15%; intervention cost USD 45; averts 108 SIDS deaths annually at an estimated cost of USD 210,500 per life saved
Ruger 2008 **[137]**	CUA	Incremental cost per LY; incremental cost per QALY	Societal / lifetime for the mother; first year of life for the infant / costs and QALYs at 3%	Lifetime cost savings due to maternal illness and cost savings due to infant illness in first year of life; varying smoking	For smoking cessation, MI cost more but provided no additional benefit compared to UC, therefore MI was dominated by UC; MI intervention did prevent relapse more effectively than UC with an estimated ICER of USD 628/QALY

				status data; varying intervention costs; varying QALY weights	
Shipp 1992 **[65]**	CBA	Break even cost	Provider / within-pregnancy / no discounting	Prevalence of smoking; intervention quit rate; spontaneous quit rate; probability of LBW; probability of maternal outcomes	Break even cost of USD 32 per pregnant woman; varying between USD 10 and USD 237 in sensitivity analyses
Tappin 2014 **[196]**	CEA, CUA	Incremental cost per quitter, incremental cost per QALY	Societal / within-pregnancy and lifetime / discounting costs and QALYs at 3.5%	Inclusion of smoking related disease costs; discount rate of 0%; risk of relapse at three months postpartum varied between 30% and 80%	Intervention quit rate of 23% vs 9% for controls; ICER of £1,127 per quitter; ICER of £482 per QALY for lifetime; 70% of cost-effective at £20,000-£30,000 WTP; additional research cost-effective if less than £3.3 million at £30,000 WTP

Taylor 2009 **[139]**	CUA	Incremental cost per QALY	Societal (implied) / lifetime / discounting costs and QALYs at 3.5%	Varying costs of each intervention between £0 and £1,000	For both mother and infant (per QALY), cognitive behaviour therapy ICER £4,005; stages of change ICER £3,033; feedback ICER £1,992; pharmacotherapies ICER £2,253; rewards and other interventions were dominant over control
Thorsen 2004 **[207]**	CBA	Cost of intervention versus cost saved	Provider (implied) / pregnancy and six months postpartum / no discounting	None	If the intervention costs USD 15,366 it would achieve savings of USD 137,592
Ussher 2014 **[195]**	CEA	Incremental cost per quitter	Societal / within-pregnancy / no discounting	Uncertainty explored by using non-parametric bootstrapping on costs and effects; halving and doubling the number of participants per fixed cost; sub-group analysis on age and cigarette	Intervention quit rate of 7.7% versus 6.4% for controls; intervention cost £35 less per patient than control therefore dominant; high degree of uncertainty with CEAC suggesting that the probability of intervention being cost-effective was 0.8 at £50,000 WTP

				dependence	
Windsor 1988 **[208]**	CBA	Incremental cost per quitter	Provider / within-pregnancy / no discounting	Varying effectiveness of guide; varying cost of staff time; varying of intervention cost	Standard information cost per person USD 2.08; quit rate of 2%; ICER USD 104.00; ALA manual cost per person USD 7.13; quit rate of 6%; ICER USD 118.83; pregnant woman's guide cost per person USD 7.13; quit rate of 14%; ICER USD 50.93
Windsor 1993 **[69]**	CBA	Benefit-cost ratio	Provider (implied) / lifetime / no discounting	Cost of intervention varied USD 4.5 - USD 9.0; smoking attributable risk of LBW varied from 0.2 to 0.15; low and high estimate of smoking attributable LBWs	LBW costs USD 9,000 to USD 23,000; cost-benefit ratio low estimate is USD 1:17.93 and high estimate is USD 1:45.83; net benefit minus cost difference is USD 365,728 (low estimate) and USD 968,320 (high estimate)

12.4 Risk of bias assessment tool as used in Chapter 4 to grade quality of included studies

This risk of bias tool was adapted from the Cochrane Handbook of Systematic Reviews. [236]

Domain	Method and statement of clear / unclear etc
1. Selection Bias Random sequence generation Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	
Allocation concealment Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	
Patients taking part Is there a large/significant difference in the proportion of possible participants and those that took part in the trial/were randomised? Was there any potential bias caused by major differences between treatment arms? Was there anything about the individuals taking part which could have led to bias in the overall estimate of relapse?	
2. Performance Bias Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).* Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	
3. Detection Bias Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes)*. Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	
4. Attrition Bias Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).* Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where	

reported, and any re-inclusions in analyses performed by the review authors.
Has an intention to treat analysis been conducted, and if yes, has it been conducted correctly/appropriately?
Were patients lost to follow up treated as smokers?
5. Reporting Bias
Selective reporting
State how the possibility of selective outcome reporting was examined by the review authors, and what was found.
6. Other Bias

Was biochemical validation undertaken? If yes, was biochemical validation undertaken post childbirth?

12.5 Summaries of trials referred to in Chapter 4: Smoking abstinence in the postpartum period after receiving a smoking cessation intervention

Table 12.5: Table of excluded studies

Author/ year	Method	Participants	Interventions	Outcomes	Reasons for exclusion
Albrecht 2006 **[1101]**	RCT	Pregnant teens aged 14 to 19 years; within 12 to 28 weeks gestation, literate in English; smoking at least one cigarette per day; single marital status; no previous live births; access to telephone. Recruited from five hospital- and two community-based prenatal clinics.	Control group: advice at clinic to stop smoking and educational materials. Meeting lasted 45 to 60 minutes, and received an incentive for attending. Intervention group one: TFS intervention, an eight week program using cognitive behavioural therapy techniques to promote and maintain abstinence. Also included a peer support program, whereby a peer was chosen from the same year as the teen to provide support and sanctions. Intervention group two: same TFS intervention; however the	Biochemically validated smoking using either salivary cotinine (cut off ≥10ng) or urinary cotinine (cut off ≥15 ng/mU) at baseline; eight weeks post randomisation, and one year following study entry.	Data presented in an unusable format and no contact with the author established. No end of pregnancy time point.

			teen chose a non-smoking peer to aid their cessation.		
Britton 2006 **[1102]**	Quasi-experimental design, control recruited first 15 months, experimental in next 17 months	Women were less than 16 weeks gestation, self-reported smoker at onset (includes recent quitters), recruited from seven obstetric offices and one medical centre in western New York, USA	Control: received standard prenatal care, may have included cessation information and tobacco use assessment. Intervention: enrolled in 'Smoke Free Baby and Me' program, nurses used 'Make yours a Fresh Start Family' program, involving tailored health message, readiness to quit assessment, kit (including calendar, booklets and distractors), action plan and quitting advice following visits.	Urinary cotinine (cut-off 200ng/ml) at first visit, 16 weeks and 28 weeks gestation and postpartum. Self-reporting at 16 and 28 weeks and postpartum visits.	No details on when postpartum visit undertaken; data presented in an unusable manner
Byrd 1993 **[1103]**	RCT	Pregnant women currently smoking, English speaking and reading, able to give free consent, expecting to live in Milwaukee following	All received usual care, involving a discussion of impacts of smoking on mother and child, plus a booklet or videotape taking around 11 minutes to read/watch. Intervention: Provided with nurses'	Self-reported status at one month post intervention, end of pregnancy and one month postpartum. Abstainers were	Intervention and control group results grouped together.

		delivery; recruited from community based obstetrics/gynaecology clinics in Milwaukee	counselling based on the Four A model: Ask, Advise, Assist, Arrange	asked to provide CO samples, but less than 20% did, results were excluded.	
Cinciripini 2000 **[1104]**	RCT	Women aged ≥18 years, more than three cigarettes a day; less than 30 weeks gestation; working video cassette player; willing to set a cessation date within two weeks of screening; not involved with any other cessation program. Recruited from Houston and surrounding metropolitan area, USA.	Both control and intervention groups received a Quit Calendar and Tip Guide. Quit Calendar showed name, quit date, and various health risk information and cessation tips. Tip Guide contained six, one page sections, outlining the major points included in the intervention video tapes. Intervention consisted of six 25-30 minute videos, covering topics ranging from initial quitting to relapse prevention and featured vignettes, peer commentary, and professional experts.	Biochemically validated abstinence using salivary cotinine (cut off ≤30 ng/ml) at quit date (two weeks after recruitment), end of treatment (four to five weeks after quit date), and one month postpartum.	No data reported at end of pregnancy.
Cinciripini 2010	RCT	Women aged more than 16 years, less than 32	All received 10 individual counselling sessions, lasting 60 minutes:	Abstinence data collected at in-clinic	Abstinence not reported for end of pregnancy.

[1105]	weeks pregnant, and smoked at least a puff or more during the past 7 days; Texas, USA.	consisting of 15 minutes of standard behavioural and motivational cessation counselling, plus 45 minutes of either the Health and Wellness intervention (control) or Cognitive Behavioural Analysis System of Psychotherapy (intervention). Health and Wellness intervention aimed to educate women on ways to decrease stress, respond to stressful events, and take care of themselves physically during pregnancy. Modules on stress management, pregnancy symptoms, postpartum depression, relaxation, optional topics including sleep, exercise, yoga, time management, parenting tips, and dealing with anger, negative thoughts and feelings. Cognitive Behavioural	visits (Visits 1-10, three and six months postpartum), and by telephone at two weeks postpartum and two, four and six weeks post end of treatment. Abstinence measured as seven day point prevalence, continuous (end of treatment to future time point), and prolonged abstinence (end of treatment to three month and six month postpartum), Seven day point prevalence

			Analysis System of Psychotherapy: a problem-solving exercise creating awareness of the relationship between their behaviour and outcomes in stressful interpersonal situations. Participants identified a recent, distressing situation, and whether their desired outcome was achieved; with the therapist's aid, participants then modified their interpretation, their behaviour and/or desired outcome, increasing the likelihood of achieving their desired outcome.	biochemically validated by expired carbon monoxide (<4ppm) or cotinine (<15 ng/ml) at visits 1-10, three and six months postpartum.	
Culp 2007 **[1106]**	Quasi-experimental – cluster (assigned control/intervention by site)	Women less than 28 weeks gestation, smokers and non-smokers, recruited from 12 rural counties health departments	Control: not defined. Intervention: Community-Based Family Resource and Support (CBFRS) Program involves curriculum on maternal health, infant health and safety and child development and parenting,	Self-reported abstinence collected at baseline, 6 months postpartum and 12 months postpartum.	Non-smoking women included, no cessation intervention, no end of pregnancy data

			including advice on smoking, delivered in a series of home visits.		
De Vries 2006 **[1107]**	Cluster RCT of four provinces, Netherlands.	Women not pregnant more than twice, able to speak and understand Dutch, smoked at least one cigarette a day, approximately 12 weeks gestation.	Control group received usual care (not defined) and a folder from the Dutch Smoking and Health Foundation. Intervention consisted of a video, self-help manual, partner booklet on non-smoking, and health counselling by midwives. Self-help guide was stage matched, focusing on pregnancy specific material and the dangers of relapsing after pregnancy. Partner's booklet focused on health impacts of the father's smoking on the child.	Self-reported seven day abstinence and continuous abstinence at six weeks post intervention and six weeks postpartum.	No end of pregnancy data
El-Mohandes 2011 **[220]**	RCT	Women aged ≥18 years, English speaking, less than 29 weeks gestation, and of an ethnic minority, recruited from	Control group: usual care, not defined. Intervention: consisted of 10 sessions (eight delivered prenatal and two postpartum) on a stages of change technique. Each session was	Biochemically validated abstinence using salivary cotinine (cut off ≤10 ng/ml) at baseline, 22-26	Trial results were unreported.

		Washington DC, USA.	approximately 35 minutes long. Women encouraged to avoid triggers, use alternative coping strategies, address active and passive smoking.	weeks gestation, 30-34 weeks gestation, and eight to ten weeks postpartum.	
Emmons 2000 **[1108]**	Quasi-experimental, 12 months control followed by 12 months intervention	Smokers or non-smokers, pregnant or up to three months postpartum, at risk of poor pregnancy outcome, low birth weight or complications	All: usual care of standard cessation 'Healthy Baby program (HBP)', strong recommendation to quit. Intervention: incorporated into regular home visits; MVI approach including nicotine level feedback, strategy for smoke reduction, feedback on nicotine levels and smoking discussed at all further visits.	Biochemically validated seven day point prevalence at six week prenatal visit and one month postpartum. Household nicotine levels and maternal salivary cotinine collected at each assessment.	No end of pregnancy data
Ershoff 1983 **[204]**	Quasi-experimental; control recruited then intervention group	Women included if less than 24 weeks gestation, elementary English speakers, smokers or	Control: standard prenatal care from Maxicare, but could choose the intervention; Intervention: group-based eight week home	Telephone interviews conducted approximately 2 months postpartum,	No end of pregnancy data, control groups also received intervention, data reported in non-

		recent-quitters (quit on learning of pregnancy), recruited from Maxicare, Southern California	correspondence smoking cessation program adapted from American Cancer Society, involved booklets on preparing to quit, quitting and maintaining abstinence, and motivational telephone answerphone system	self-reported only	usable format.
Haug 1994 **[1109]**	RCT	Women aged 18-34 years, daily smoker; recruited from GPs in Norway, half pregnant and half non-pregnant	Control group received usual care; details not given. Invention: told to stop smoking, received one session by GP up to 15 minutes and two booklets.	Blood test for serum thiocyanate at first visit and 12 months post-intervention, questionnaire at 18 months; point prevalence data at six, 12, 15 and 18 months post-intervention	No end of pregnancy data
Hotham 2006 **[1110]**	RCT	Women smoking at least 15 cigarettes daily (biochemically confirmed	Control: counselling via QUITR organisation involving brochures, quit date negotiation, discussion of	CO measurement at start of intervention (over 8 p.p.m) and at	No postpartum data.

		by CO measurement), between 12 and 28 weeks gestation, interest in quitting, recruited in Women and Children's Hospital, Adelaide, Australia	smoking habits and support options, including healthy eating. Intervention: Offered nicotine patches (15mg/16h) for maximum of 12 weeks, optional weaning to lower strength	last antenatal visit; telephone contact at six weeks and three months, self-reported only	
Hughes 2000 **[1111]**	RCT	Infertile and pregnant women who smoked three or more cigarettes in last six months; recruited from University of Michigan Centre, Henderson Hospital, and St James' Hospital, Hamilton, Ontario, Canada	Control: standard information available at clinics on impacts of smoking. Intervention: scripted five point stages-of-change intervention: 1) pre-contemplation, 2) considering quitting, 3) preparing to quit 4) quitting 5) maintaining cessation. Booklets given out at each session along with further encouragement.	CO breath monitoring conducted at enrolment, six and 12 months after enrolment. Cut-off not reported; questionnaire conducted at 12 months after follow-up	No end of pregnancy data, postpartum data in unusable format
Kientz 2005 **[1112]**	N/A	Women aged 18 or older, stopped smoking by 36 weeks gestation.	Control: not defined. Intervention: received the Kientz Interventions for Continued Cessation of Smoking,	Self-reported smoking at 7-14, 14-28, and 28-42 days	Relapse prevention intervention, delivered in the postpartum period.

			consisting of personalised, stage-matched interventions delivered from the 36th week of pregnancy to sixth week postpartum, including reading materials, hard candy, and follow up phone call.	postpartum, and six weeks postpartum.	
Langford 1983 **[1113]**	RCT	Women attending pre-natal classes, approximately seven months pregnant and current smokers	All received regular antenatal classes. Intervention 1: received a 30 minute presentation and pamphlet on smoking during pregnancy. Intervention 2: Received intervention 1 plus a home visit by nurse to reinforce presentation.	Self-report only. Collected immediately before intervention, four months and one year after delivery.	No end of pregnancy data.
Mayer 1990 **[1114]**	RCT	Currently smoking pregnant women; recruited in Grand Rapids, USA	Control: received printed information on risks of smoking in pregnancy and usual care (not defined). Intervention 1: Multiple Component group – received 20 minute one-to-one session including risk information and behaviour change, adapted from	Biochemical validation (saliva thiocyanate) only conducted on last third of trial.	No fixed time point for postpartum data. Attempted contact with author but no response.

			'Because I Love my Baby' materials, which involved agreeing an individual behavioural contract and self-monitoring charts with action plan. Intervention 2: Risk information group: received face-to-face session of approximately 10 minutes, provided with factual brochures but no self-help or behavioural change information.		
McBride 1999 **[1115]**	RCT	Women less than 20 weeks gestation, current smoker or recent quitter (within 30 days prior to recruitment).	All groups received self-help booklet entitled 'Stop Now for your Baby'. Contained information about health effects of smoking during pregnancy, suggestions for quitting, stress reduction techniques, and behavioural alternatives. Both intervention groups received personalised letters and relapse prevention kits, consisting of a	Biochemically validated smoking using salivary cotinine (cut off ≤20 ng/ml) at 28th week gestation, six and 12 months postpartum.	Unable to separate women who had smoked during pregnancy from those that had quit before pregnancy.

	booklet entitled 'Balancing Act', with introductory letter. Booklet discussed transition from pregnancy to postpartum and related factors. This was mailed after completing 28th week follow up. Intervention group one: prenatal telephone counselling consisting of three calls, first approximately two weeks after self-help booklet mailed, and the remaining at monthly intervals. Telephone calls delivered by trained counsellors, and followed a standardised protocol using motivational interviewing and stages of change techniques. Calls lasted approximately 8.5 minutes. Intervention group two: an additional three calls within the first four months postpartum. Calls reinforced

			themes from relapse prevention booklet; first call scheduled within four weeks after delivery; the rest following at four to six week intervals. Calls lasted on average 7.7 minutes. Also received series of postpartum newsletters at two, six and 12 weeks postpartum.		
McBride 2004 **[1116]**	RCT	Women less than 20 weeks gestation, current smokers or recent quitters (within 30 days prior to pregnancy but not smoking at intake), living with an intimate partner, willing for partner to be contacted for study. Women recruited from the Womack Army Medical	All groups received usual care, consisting of self-help booklet 'Makes Yours a Fresh Start Family', written at a fifth grade reading level by the American Cancer Society. Intervention one: late pregnancy relapse prevention kit consisting of a booklet and gift items, and six counselling calls. Calls delivered by a health advisor using motivational interviewing techniques. Three conducted during pregnancy and	Self-reported abstinence at the 28th week gestation, three, six and 12 months postpartum. Biochemically validated abstinence at 28 weeks gestation and six months postpartum, method and cut off not stated.	Women who had quit before pregnancy included; unable to separate from women who had smoked up to and during pregnancy.

		Centre, Fort Bragg, Fayetteville, North Caroline, USA.	three postpartum, last one no later than four months postpartum. Calls at monthly intervals. Intervention two: partner expected to assist. Received 'It takes two' booklet and companion video. Partners received six calls from the woman's health advisor, using a similar motivational interviewing technique. Three delivered during pregnancy and three postpartum. Smoking partners given self-help guides, free nicotine patches, and stage appropriate counselling.		
Parker 2007 **[206]**	RCT	Smoked one puff in last 30 days, no more than 26 weeks pregnant, access to a telephone, spoke English or Spanish. Recruited from urban	All received self-help materials which included a quit kit and a video. Both intervention groups: enrolled on a quit and win monetary incentive lottery program. Eligibility for prize of USD 100 restricted to smokers who	Biochemically validated abstinence using urinary cotinine (cut off ≤80 ng/ml) at 32 weeks gestation and six months	Data from only one arm of the second intervention arm of the trial reported.

		prenatal clinics in Rhode Island, Connecticut, and Massachusetts, USA.	reported abstinence for at least 30 days, confirmed by urinary cotinine. Intervention two: up to three motivational interview calls; to discuss smoking habits, maternal and foetal health risks, readiness to change, and encourage use of intervention materials.	postpartum.	
Patten 2010 **[1117]**	RCT	Women aged 18 years or older, less than 24 weeks gestation, self-reported smoking in last seven days, planning to quit within next 30 days, access to telephone and a video/DVD player. Women were recruited from Yukon–Kuskokwim Delta in Western Alaska, USA.	Control group received a counselling based intervention utilising the 5 As; Ask, Advise, Assess, Assist, and Arrange. Session conducted at first visit and lasted five minutes. All received four pregnancy brochures. Intervention participants received the cessation guide, and 15-25 minute counselling session based upon the 5 As. Also privately shown a video, followed by 10-15 minute discussion with the counsellor. Video	Biochemically validated abstinence using salivary cotinine (cut off ≤ 20 ng/ml) at baseline and end of pregnancy.	No postpartum outcomes.

			provided for home use. Also scheduled four 10-15 minute telephone sessions at weeks one, two, four, and six. Women encouraged to set a quit date at each session.		
Pbert 2004 **[1118]**	Cluster RCT – health centres were randomised.	Women who spoke English or Spanish, at least two months before due date, current smoker or spontaneous quitter (quit after learning of pregnancy), planning to remain in the area for at least six months following delivery. Women recruited from six community Health Centres in the greater Boston area,	Control group received usual care, not defined. Intervention: to change delivery of cessations services at community health centres. Consisted of training to deliver an intervention using national best practice guidelines and stages of change techniques; an office based management system to routinely screen smoking status, prompts to intervene, document encounters, distribute materials, and arrange follow ups. Establishment of program boards to coordinate transfer of	Biochemically validated abstinence using salivary cotinine (cut off ≤20 ng/ml) at baseline, nine month of pregnancy/before delivery, one month, three months, and six months postpartum.	Women who had quit before pregnancy included; unable to separate from women who had smoked up to and during pregnancy.

		Massachusetts, USA.	documentation among clinics and conduct periodic meetings with all clinic representatives.		
Peden 2008 **[1119]**	Quasi-experimental	Pregnant women who were ≤ 25 weeks gestation, 18 years old or over, current smokers or recent quitters within the last nine months, access to a telephone	Control: no intervention. Intervention: Received four 90 minute group sessions targeting negativity and making affirmations to quit with post-session reinforcement. Received six postpartum telephone calls once a week, starting at one week postpartum.	Urinary cotinine at baseline (cut-off 100ng/ml). Self-reported data collected at one month post-intervention, two and four months postpartum.	Results for controls and interventions combined; no end of pregnancy data
Peterson 1992 **[1120]**	Part RCT and part cluster: Three sites randomised between control and intervention group one; one site allocated to intervention group	Pregnant women who were literate and English speaking	All participants received pregnancy related health education materials. Control group: received routine obstetric care and mailed a list of community-based cessation resources. Intervention group one: mailed the pregnancy specific self-help manual and audiocassette tape.	Biochemically validated abstinence (cut off 80 ng/mL using urinary cotinine) at six months gestation. Self-reported smoking status at	No end of pregnancy data.

	two.		Intervention group two: same materials as group one, obstetricians and practice nurses attended a session reviewing current research and guidelines, a progress sheet included in the patient's medical records, patients reinforcement letters signed by their physicians during eighth month gestation and one month postpartum.	eight weeks postpartum.	
Polanska 2004 **[1121]**	Cluster RCT	Pregnant women who were either smokers or spontaneous quitters. Public maternity centres in Kodź, Poland.	Control group: standard written information about the health risks from smoking during pregnancy and the benefits of quitting. Intervention: four visits by midwife to participant's home. Women received translated written materials prepared by the Community Health Research Unit in Ottawa. A further five visits were offered to those still smoking at the	Self-reported abstinence at end of pregnancy and one year postpartum.	Could not split women who had quit before pregnancy from those smoking during pregnancy in the control group.

			fourth visit. Spontaneous quitters received information on how to avoid smoking and relapse.		
Reitzel 2010 **[1122]**	RCT	English speaking, aged 18 years or older, who stopped smoking either during their pregnancy or within two months prior to pregnancy.	All participants received self-help materials and five to 10 minutes of relapse prevention advice. Intervention one (MAPS intervention): six telephone counselling sessions delivered at weeks 34 and 36 gestation, and two, four, seven, and 16 weeks postpartum. Intervention two (MAPS+): identical to MAPS, with two additional calls at baseline and eight weeks postpartum.	Biochemically validated abstinence using either carbon monoxide (cut off ≤10 ppm) or salivary cotinine (cut off ≤20 ng/ml) at eight weeks and 26 weeks postpartum.	Women who had quit before pregnancy unable to separate from those that smoked during pregnancy; no end of pregnancy data; relapse prevention intervention.
Ruger 2008 **[137]**	RCT	Less than 28 weeks gestation, receiving prenatal care, current smoker or not smoking within 3 months of	Control: standard prenatal care including five minute interview and self-help materials. Intervention: MVI in home visit format, three one hour visits on average tailored to stage of	Biochemically validated abstinence at baseline, one month after intervention and six	No end of pregnancy data

		baseline, English or Spanish speaker, no inpatient drug treatment; recruited from hospital and health clinics in Boston area, USA	readiness. Involved impact of smoking education, smoking behaviour evaluation, self-efficacy improvement, goal setting and household nicotine feedback. Also received self-help materials	months postpartum (salivary cotinine level, cut-off not reported).	
Strecher 2000 **[1123]**	RCT	Women smoked 100 cigarettes or more in lifetime, current smokers or quit since becoming pregnant, recruited from obstetrics and gynaecology clinics at Universities of Michigan and North Carolina, USA	Control: Received 'A pregnant woman's guide to quit smoking' after first visit. Intervention: tailored cessation messages after each prenatal visit, personalised guide and quit plan based on responses to questionnaires after each visit. Updated guide sent out each time new interview completed.	Urine samples collected at prenatal visit, 24th week of pregnancy and six weeks postpartum. Self-reported abstinence at three months postpartum.	No end of pregnancy data; smokers and recent quitters grouped together
Tuten 2012 **[1124]**	RCT	Over 18 years old, less than 30 weeks gestation, smoked more than 10 cigarettes daily, capable of informed consent;	Control: information on adverse effects of smoking, educational materials, routinely asked about status at follow-up, compensated for urine and breath samples. Incentive	Biochemical validation at baseline using exhaled CO and urinary cotinine (cut-off 200 ng/ml). Self-	No end of pregnancy data

		recruited from Center for Addiction and Pregnancy, Hopkins Bayview Medical Campus, Baltimore, USA	1: increasing financial incentives based on meeting abstinence targets, from USD 7.50 to a maximum of USD 41.50, reset to base level if target not met, returned to previous level if met five times consecutively. Intervention 2: pre-determined incentive schedule not dependent on individual smoking status, patients required to submit samples for eligibility; received incentives for up to 12 weeks or until delivery	reported at one and three months after enrolment and six months postpartum.	
Valanis 2001 **[1125]**	Quasi-experimental – historical comparison, interim controls and intervention group	Smokers (at least one cigarette in the last seven days before prenatal visit), or recent quitters (smoked in the month before conception but not in last seven days); recruited from six	Control: discussed smoking and its impacts with expectant mothers. Interim: usual care but may have received some intervention Intervention: At first prenatal visit, used MVI based on FRAMES model: Feedback, Responsibility of patient, Advice, Menu of strategies, Empathy,	Data obtained via questionnaire one year postpartum	Smokers and recent quitters not separated

	prenatal clinics, two hospitals, and seven paediatric clinics in Portland, Oregan, USA	Self-efficacy in quitting. Action plans created and updated in subsequent visits. Relapse prevention messages delivered in hospital or at 3-day postpartum visit, nurses continued to work with smoking mums postpartum at well-baby clinics.		

Table 12.6: Table of included studies

Author/ year	Method	Participants	Interventions	Outcomes	Notes
Bullock 2009 **[248]**	RCT	Women attending 21 rural Women Infant and Children Nutritional Supplement clinics in a Midwest state.	Usual care group: Quit Smoking for Good pamphlet from the American Heart Association. Intervention group one: social support (baby BEEP) plus booklets, a scheduled weekly telephone call and 24 hour access to the nurse for additional social support. The eight booklets comprised a program called ''Stop Smoking! A Special Program for Pregnant Women'' adapted to a 7th grade reading level. Intervention group two: social support alone. Intervention group three: the booklets alone.	Primary outcomes: point prevalence abstinence (cut off cotinine <30 ng/ml) in late pregnancy and 6 weeks post-delivery.	
Cooper 2014 **[123]**	RCT	Women aged 16 to 50 years, between 12 and 14 weeks pregnant, smoking at least 10 cigarettes daily before	All participants: midwife delivered behavioural support counselling for one hour, involving advice and tips for cessation, requirement to set a quit date in two weeks' time. Midwives provided three further	Primary outcomes: biochemically validated sustained abstinence (carbon monoxide ≥8 ppm) at one month after	One woman removed from the placebo group after being recruited to the study twice.

	pregnancy and currently smoking at least five per day; exhaled carbon monoxide concentration of at least eight p.p.m. Women excluded if they had diseases which could be affected by NRT (cardiovascular disease, unstable angina, cardiac arrhythmias, skin disorders, known sensitivity to NRT), known drug or alcohol dependence, known major foetal	support sessions after quit date. Telephone support conducted on the quit date, three days, and one month afterwards. Could also contact NHS Stop Smoking Services for additional support. The intervention group received a four week supply of 15mg/ 16 hour nicotine replacement therapy transdermal patches. The control group received visually identical placebo patches. Women told to start using the patches on their quit dates. One month after quitting, those biochemically identified as not smoking were issued with another four week supply of NRT/placebo patches if requested.	quit date and delivery. Secondary outcomes: biochemically validated point prevalence abstinence at one month after quit date, and at delivery. Self-reported point prevalence and sustained abstinence at one month after randomisation, at delivery, six months, one year, and two years postpartum.

		abnormalities, or unable to give informed consent.			
Donatelle 2000 **[249]**	RCT	Women aged 15 years or older, 28 weeks gestation or less, and self-reported smoker, Oregon, USA.	All participants: verbal and written information on the importance of cessation, and received self-help kit "A Pregnant Woman's guide to Quit Smoking". Intervention group: three pronged program involving positive incentives, social support, and community participation. Included financial incentive vouchers of USD 50 a month for confirmed quitters, and financial incentive vouchers (USD 50 in first and last months of the trial, USD 25 for the month in-between) for the social supporter.	Biochemically validated status (salivary thiocyanate (<100 ug/ml)) at end of pregnancy and two months postpartum.	
Dornelas 2006 **[202]**	RCT	Women aged 18 or over, 30 weeks gestation or less, access to telephone, no recent history of	All participants: standard cessation treatment comprising: an educational booklet and chart prompt reminding providers to give personalised quit message at each visit, with cessation advice from an.	Biochemically validated status using carbon monoxide (<4ppm) at end of pregnancy and 6 months postpartum	33 women who had quit before baseline along with two people with missing data

		alcohol, substance abuse, or psychiatric illness, recruited from prenatal tertiary care clinic, Hartford, Connecticut, USA	obstetrician, gynaecologist or nurse. Intervention: One 90 minute psychotherapy session, plus bi-monthly calls during pregnancy and monthly calls post-delivery by trained mental health counsellors.		excluded.
Dunkley 1997 **[244]**	RCT	Women ≤ 18 weeks gestation, smoking one or more cigarettes daily, maternity units in teaching hospitals, UK	Control: No intervention Intervention: midwives trained in and delivered five stages of change intervention: pre-contemplation, contemplation, ready for action, action and maintenance	Self-reported data; end of pregnancy and one month postpartum	
Gielen 1997 **[245]**	RCT	Women who had smoked a puff within seven days, 27 or less weeks gestation, African-American or white, large prenatal clinic, Baltimore, USA	All received advice from nurse pre-and postpartum on risks of smoking and recommended to quit, plus pamphlets. Intervention: received 'A pregnant woman's guide to quit smoking' with sixth grade reading level, 15 minute one-to-one counselling session on the guide and educational materials, clinic reinforcement	Saliva Cotinine (cut off not reported) only on self-reported quitters at first prenatal visit, over 28 weeks gestation, end of pregnancy, three and six months postpartum.	76 women excluded due to miscarriage, abortion or withdrawal

			including verbal support, written prescription given at each prenatal visit; two letters of encouragement mailed 1-2 weeks after first visit.		
Hajek 2001 **[259]**	Cluster RCT – individual midwives randomised	Women who were current smokers or recent ex-smokers (within last 3 months), nine hospital and community trusts, UK	Control: access to standard smoking leaflets. Interventions: those not planning to change received 'Choice is yours' booklet. Smokers aiming to quit and recent ex-smokers also given advice including CO analysis and booklet 'How to stop smoking for good'/'How to stay off smoking for good' respectively, followed by quiz, interview, and commitment statement. 'Buddy' support system pairing with other pregnant smokers encouraged. Midwives received additional training: one hour for control, two hours for intervention.	Biochemically validated (Carbon Monoxide ≤10 p.p.m) continuous abstinence at end of pregnancy and six months postpartum	167 women were excluded due to adverse pregnancy outcomes or moved away.
Heil 2008 **[250]**	RCT	Women who self-reported smoking in last 7 days, were 20 weeks or less	All participants: usual care involving discussing the advantages of quitting during pregnancy, and two pamphlets designed specifically for pregnant women, distributed	Biochemically validated point prevalence and continuous abstinence at end of pregnancy, 12	

		gestation, English speaking, residing in the greater Burlington area, US.	during pregnancy and after delivery. Control group received non-contingent vouchers which were independent of smoking status. Voucher values were USD 15 per visit antepartum and USD 20 postpartum. Intervention group received vouchers based upon biochemical validation results, reporting breath CO specimens <6ppm or urine cotinine levels <80 ng/ml. Vouchers began at USD 6.25, and increased by USD 1.25 per consecutive negative specimen, to a maximum of USD 45. A positive or missed report reset the voucher to the beginning, though it was restored if the next two samples were negative.	weeks, and 24 weeks postpartum.
Hennrikus 2010 **[251]**	RCT	Women in the first or second trimester, current smoker, at least 18 years old,	All participants: in-person session designed to increase motivation to quit and provide information about community cessation resources. Intervention group received additional monthly telephone sessions and	Biochemically validated seven day point prevalence (urinary cotinine (<100 ng/ml)).

		Minnesota, USA.	their supporter also contacted.	
Hjalmarson 1991 **[264]**	Quasi randomised - allocated by days born in month, 1-10 of every month allocated to controls and 11-31 allocated to treatment.	Self-reported daily smoking pregnant women, less than 12 weeks gestation, 13 public health clinics, Gothenburg, Sweden.	Control group received an information sheet which included basic facts about smoking and pregnancy and recommended to quit. Intervention group: self-help manual written for pregnant women, which included a task based upon behavioural therapy, information and advice on how to keep abstinent, and basic facts about smoking and pregnancy.	Biochemically validated (blood thiocyanate ≤100ng/ml) point prevalence at week's 30-34 gestation, at hospital, and eight weeks after delivery.
Lawrence 2003 **[262]**	Cluster RCT, randomised by antenatal clinics.	Women aged 16 or over, current smoker, English speaking, West	Control group: standard smoking cessation advice currently given by midwives. All participants received the booklet "Thinking	Biochemically validated (urinary cotinine <1.5 ug/l) point prevalence

	Midlands, UK.	about stopping". Midwives in control group received half a day's training on the research protocol only. Midwives in intervention group A received two and a half days training, with two days on the theory of the transtheoretical model, aimed to aid midwives deliver the stages of change model. Also received the same training on the research protocol as the control group. Participants received a set of six, 30 page stage based self-help manuals, entitled "Pro-change programme for a healthy pregnancy". At three points during pregnancy, midwives assessed a participant's stage of change, highlighted the appropriate manual in the stage series, and spent no longer than 15 minutes ensuring the participant was familiar with how to use the materials. Midwives in intervention group B received the same training as group C, and the participants	abstinence at 30 weeks pregnancy, and 10 days after pregnancy. 18 months point prevalence and 18 months continuous abstinence from self-reported data only.

			received the same self-help manuals as group B. Additionally, participants used a computer programme on a laptop for each intervention in the manual. Women worked alone, and feedback was printed and sent to the participant within one week of each intervention.		
Lillington 1995 **[260]**	Cluster RCT – site of program randomised	Women 18 years old or more, current and ex-smokers; Los Angeles, USA	Control: usual care including printed information on risks of pregnancy and group quit messages as part of initial visit. Intervention: 'Time for Change' with four components: 1) one-to-one counselling session, 2) self-help guide, 3) reinforcement booster cards (mailed one month after study entry), 4) incentive contest (weekly draw of USD 100 worth of baby items). Available in English and Spanish at third grade reading level.	End of pregnancy self-report only. Salivary cotinine (≤20ng/ml) at six weeks postpartum.	Participant with missing data excluded from analyses
McLeod 2004 **[263]**	Cluster RCT - midwives	Midwives eligible if they planned to	Control group: usual care from the midwives, which consisted of anything from just asking	Point prevalence was self-reported at six	

	stratified by geographical location.	continue practising for the next 12 months. Eligible women reported smoking when registering with the midwife for maternity care. North Island of New Zealand.	to providing more detailed cessation advice. Intervention group A: a programme of education and support for cessation or reduction, which involved using brief intervention and motivational interviewing. Training consisted of a four hour session, training videotape, and follow up problem solving sessions with a smoking counsellor. Intervention group B: a programme of education and support for breast feeding for smoking women, aimed to increase the duration of full breast feeding, with information about the effects of smoking. Training consisted of provision of information about breast feeding, discussion with a qualified lactation consultant, introduction of an information booklet, additional refresher, and problem solving sessions with a lactation consultant and/or midwife. Intervention group C: received both the smoking	weeks and four months postpartum. Biochemical validation was undertaken at 28 weeks gestation, using cotinine in serum (≤15 ng/ml).

			education and breast feeding programme, with an additional session combining the two interventions training content.		
Messimer 1989 **[261]**	Cluster RCT – individual practices were randomised	Women smoking at first prenatal visit ≤ 28 weeks gestation; Michigan and upper Wisconsin, USA	All: Counselling by physician on three occasions, suggestion to quit after each one. Discussion on nicotine effects, smoking-related complications and effect on foetus; ashtrays removed from waiting area, staff not allowed to smoke in view of patients. Intervention: use of 'Because you you're your baby' flipchart, packets and poster; monitoring of smoking at each visit with encouragement to quit, presentation at first visit.	Self-reported data at end of pregnancy and six weeks postpartum	Women with adverse pregnancy event (abortion, miscarriage), moved away, or incomplete data excluded.
O'Connor 1992 **[265]**	Quasi-randomised using an alternate day strategy.	Women reporting smoking daily and less than 31 weeks gestation; Canada.	All participants received usual care: three to five minute verbal explanation of the hazards of smoking during pregnancy, invitation to a two hour group cessation class using a self-help guide. Classes were conducted in the evening by a public health nurse, in English or	Biochemical validated (≤64 ng/mL urinary cotinine) status at 36 weeks gestation and six weeks postpartum.	

			French, and a nurse was available for one follow up contact. Intervention group also received the option of Windsor's self-help smoking cessation program during the visit to the clinic. A 20 minute intervention was provided on an individual basis, in English or French, by a public health nurse, with the offer a telephone follow up contact at a mutually agreed upon time.		
Oncken 2008 **[252]**	RCT	English or Spanish speaking women, 26 weeks gestation or less, currently smoking at least one cigarette per day, aged 16 years or over, intending to carry the pregnancy to term. Hartford Hospital, Connecticut, New Britain,	All participants: two 35-minute counselling sessions using a motivational interviewing to aid cessation. Counselling sessions delivered at baseline and at the first visit, focusing on benefits of quitting during pregnancy, assessing the stage of change, motivating the participant to quit, and setting a quit date or reduction target within the next week. The second session occurred one week after the quit/reduction date; focused on dealing with withdrawal symptoms and urges. Also	Biochemically validated status (carbon monoxide < 8ppm) at 6 weeks post-intervention, 32-34 weeks gestation, 6-12 weeks postpartum.	The Data and Safety and Monitoring Board decided to stop enrolment at 147 patients after reviewing efficacy data at six weeks due to a larger study would be required to detect

		Connecticut, and Springfield Massachusetts.	received printed educational materials tailored for pregnancy and bi-monthly telephone calls until delivery. Control group: placebo gum. Intervention group: gum containing 2mg of nicotine. Both groups were instructed to chew one piece of gum for every cigarette per day, up to 20 pieces. Participants received six weeks of treatment followed by a six week taper period.		the anticipated difference.
Panjari 1999 **[247]**	RCT	Women less than 20 weeks gestation, either smokers or recent quitters, singleton pregnancy, the ability to speak and read English, no drug dependency. Royal Women's Hospital, Melbourne,	Control group: standard antenatal care, including distribution of a Quit Victoria pamphlet 'Smoking and Pregnancy'. Intervention group: four counselling sessions by a midwife trained in smoking cessation techniques. The first session lasted for 25 minutes, and included distribution of literature, viewing the Baby Breathing video followed by discussion of its contents, delivery of a strong verbal message about the risks of smoking during pregnancy, and	Biochemically validated status (urinary cotinine <115 ng/mL) at 30-34 weeks gestation. Self-reported smoking status at six weeks and six months postpartum.	

		Victoria, Australia.	advice to quit. Subsequent sessions usually lasted five to ten minutes, and focused on the patient's progress. Sessions delivered at 16-20, 24, and 28 weeks gestation.		
Pollak 2007 **[253]**	RCT	Women aged 18 or older, between 13 and 25 weeks gestation, five or more cigarettes a day and over 100 cigarettes in their lifetime, planning to continue prenatal care in a participating clinic, English speaking. 14 clinical sites in Durham, Raleigh, and Fayetteville, North Carolina, USA.	All participants: six counselling sessions (five face to face prenatal visits and one via telephone) designed to enhance motivation and develop skills needed to quit, a quit kit: a booklet designed for pregnant smoker:, water bottle, straws, hard candy, an exercise band, and a stress management tape. Intervention group: At first session, women were informed of advantages and disadvantages of the three types of NRT therapy (patch, gum, and lozenge), and aided in deciding which type to choose, with no NRT an option. Enough NRT given to last until the next session. Use of NRT recommended for up to six weeks, but women could choose to use it for longer. Women allowed to	Biochemical validated status (salivary cotinine) at 7 weeks post randomisation, 38 week's gestation, and 3 months postpartum, however only self-report results were reported.	Recruitment suspended early by Independent Data and Safety Monitoring Board when the interim analysis found a higher rate of negative birth outcomes in the intervention group.

			change between NRT modalities. Women who wore patches were instructed to only use them during waking hours (16 hours). The dosage was: less than 10 cigarettes a day, 7mg/day; 10 to 14 cigarettes a day, 14mg, and more than 15 cigarettes a day, 21mg/day. Those who choose the gum or lozenge instructed to use one 2mg piece for every cigarette.	
Rigotti 2006 **[254]**	RCT	Women, smoking at least one cigarette in the past seven days, 18 years or older, 26 weeks gestation or less, willing to consider altering their smoking habits, access to telephone, English speaking. Tufts Health	At enrolment, all subjects mailed a validated pregnancy specific smoking cessation booklet. Participants' prenatal care providers were sent the American College of Obstetricians and Gynaecologists smoking cessation practice guideline and a reminder to address smoking at the subjects' visits. Control participants: standardised counselling intervention of up to five minutes at the enrolment session. Smokers requesting further assistance referred to the	Biochemically validated seven day point prevalence and sustained abstinence (salivary cotinine < 20 ng/mL) at end of pregnancy and three months postpartum.

		Plan, Massachusetts.	Massachusetts telephone quit line. Intervention subjects: each subject had a dedicated counsellor offering up to 90 minutes of counselling during pregnancy and 15 minutes over two months postpartum. Calls scheduled to subject's needs. Intervention consistent with the five step cessation counselling guidelines, targeting pregnancy related issues, working towards goals, plans for cessation or reduction, and relapse prevention techniques. After initial call, subjects mailed a personalised worksheet and a summary letter and targeted written materials after each subsequent call.	
Secker-Walker 1994 **[243]**	RCT	Women less than 25 weeks gestation, smoking one or more cigarette a day.	Control group: usual advice about smoking provided by obstetrician or midwife. Intervention group: usual care and individualised cessation intervention, consisting of a series of counselling sessions,	Biochemical validated status (urinary cotinine <80 ng/mL) at 36 weeks gestation. Self-reported smoking at 8-15 months,

		Vermont, USA.	delivered by trained counsellor at first, second, and third prenatal visits, at 36 weeks gestation and six weeks postpartum. Sessions consisted of setting up a quit plan, health benefits of cessation, and a specially prepared booklet about quitting. Postnatal sessions focused on the influence of the parent on the child and its future.	16-24 months, and 24-54 months postpartum.	
Secker-Walker 1998 **[246]**	RCT	Not stated; assumed 12 years old. Maternal infant care clinic, Vermont, USA	Control: physicians prompted by sheet on chart to provide advice, strong recommendation to stop and cessation booklet for pregnant women at first visit. Intervention: at first visit physicians gave structured advice including exhaled CO analysis, strong recommendation to quit and commitment statement, combined with referral to trained nurse for individual counselling on behaviour change. Repeated at second, third, fifth visits and 36th week visit. Quitters praised and counselled for	Biochemically validated status (carbon monoxide ≤6 p.p.m and urinary cotinine ≤500ng/ml)) status at first, second and 36th week visits. Self-reported status at one year postpartum.	24 women excluded due to adverse pregnancy conditions.

			remaining quit.		
Stotts 2002 **[255]**	RCT	English speaking women aged 18 years or older, smoked more than 5 cigarettes a week, less than 20 weeks gestation. Houston and Dallas metropolitan area.	Control group unclear. Intervention group: one-to-one intervention consisting of a 20-30 minute telephone counselling session using motivational interviewing strategies, conducted at 28-30 weeks gestation, focusing on commitment to change smoking behaviour. A personalised, stages of change based feedback letter mailed within a week of first call. Letters computer generated based upon responses to first call, including individualised messages about effects of smoking on others, pros and cons of smoking, temptation to smoke, and confidence to abstain. A final motivational interview based counselling call four to five days after the feedback letter. Included discussing the letter, reassessing commitment to change, building motivation, and evaluating the change plan.	Biochemically validated status (urinary cotinine <80 ng/mL) at the 34th week gestation conducted on a sub sample of 175 out of 269 randomised. Self-reported smoking at six weeks, three months, and six months postpartum.	Unclear whether the control group received no intervention or counselling and self-help booklets before randomisation.

Thornton 1997 **[256]**	RCT	Women had to be currently smoking or spontaneously quit prior to entering prenatal care. Public antenatal clinic at Rotunda Hospital, Dublin.	All participants: routine prenatal advice on a wide range of health issues, including smoking, from the midwifery staff and obstetricians. Intervention group: face-to-face 10 to 15 minute counselling session by the stop smoking facilitator at first visit. Further counselling sessions for both the woman and her partner offered at subsequent visits. Also received an information pack consisting of a leaflet outlining the health effects of smoking on the woman and baby, an invitation to join a quitting group in the hospital, a letter to the partner to support her attempts to quit with an invitation to join the quit support groups, a self-help booklet dealing with preparing to stop and strategies to cope with withdrawal and maintaining abstinence, prompt cards 'Reasons for quitting myself' and 'Reasons for quitting for my baby', and a carbon monoxide	Self-reported smoking at delivery and three months postpartum.

			monitor to quantify smoking habits.		
Ussher 2014 **[192]**	RCT	Women aged 16 – 50 years old, 10-24 weeks gestation, currently smoking one cigarette or more daily, prepared to quit one week after enrolment, English speakers and able to walk continuously for 15 minutes or more, not dependent on alcohol or drugs. 13 hospital antenatal clinics in England	All patients: behavioural support comprising six weekly 20 minute sessions starting one week before quit date and finishing four weeks afterwards. All sessions one-to-one and face-to-face. Continuing support offered to non-quitters or relapsed smokers. Intervention: physical activity (PA), combining consultation and supervised exercise. Total of nine 20 minute consultation sessions prior to supervision, working through booklet retained by patient; encouraged to view PA as self-control strategy. Total of 14 supervised exercise sessions, twice a week for six weeks then weekly for two weeks, patients advised to aim for minimum 30 minutes continuous treadmill walking per session. Asked to log daily steps, 10% weekly increment calculated, gradually aiming for 10,000 steps.	Biochemically validated status (carbon monoxide <8 p.p.m) assessed weekly up to four weeks after quit date and at end of pregnancy; salivary cotinine (<10ng/ml) measured at four weeks post quit date and at end of pregnancy. Self-reported status at six months postpartum.	Two excluded due to sequential pregnancies and two erroneously enrolled

Walsh 1997 **[257]**	RCT	Smoking women. Antenatal clinic of an urban teaching hospital, Australia.	Control group: at first visit, patients informed by doctor and midwife that smoking was an important health issue and that they should stop. Also received a sticker, risk pamphlet for women, and two-page cessation guide. Intervention group: three minute advice session from doctor highlighting risks from smoking during pregnancy, followed by 15 minute video on risks, barriers to quitting, and cessation tips. Also received a 10 minute counselling session with midwife using the same format, setting a quit date. Received a self-help manual with four packets of gum. Social support came from an accompanying adult invited to participate. Chart reminder placed on medical record. Letter signed by midwife sent at 10 days. At the second visit and 34th to 36th visits, midwives provided five further minutes of counselling and doctors gave approximately two minutes of	Biochemically validated status (urinary cotinine <500 nmol/L) at four weeks post intervention, end of pregnancy, and six to 12 weeks postpartum.

			risk advice. Those still smoking at the last visit were advised to attend an external cessation course.	
Wisborg 2000 **[258]**	RCT	Women less than 22 weeks gestation who smoked 10 or more cigarettes per day. Denmark.	All received a 45-60 minute counselling session informing women about the pharmacologic and psychological aspects of smoking, consequences of smoking during pregnancy, and advice to quit. Also received a pamphlet on smoking and pregnancy. Further counselling at eight weeks and 11 weeks after first visit, and four weeks before due date, lasting 15-20 minutes. Control group received 11 weeks of placebo patches at first visit. Intervention group received NRT consisting of 15 mg patches for 16 hours per day for eight weeks, and 10 mg patches for 16 hours per day for three weeks.	Biochemically validated status (salivary cotinine <26 ng/mL) at fourth prenatal visit. Self-reported smoking status at second and third prenatal visit, three months and one year postpartum.

12.6 Results of meta-analysis of patterns of abstinence in the postpartum period

Figure 12.1: Primary analysis, pooled estimates of abstinence using combined data on all participants

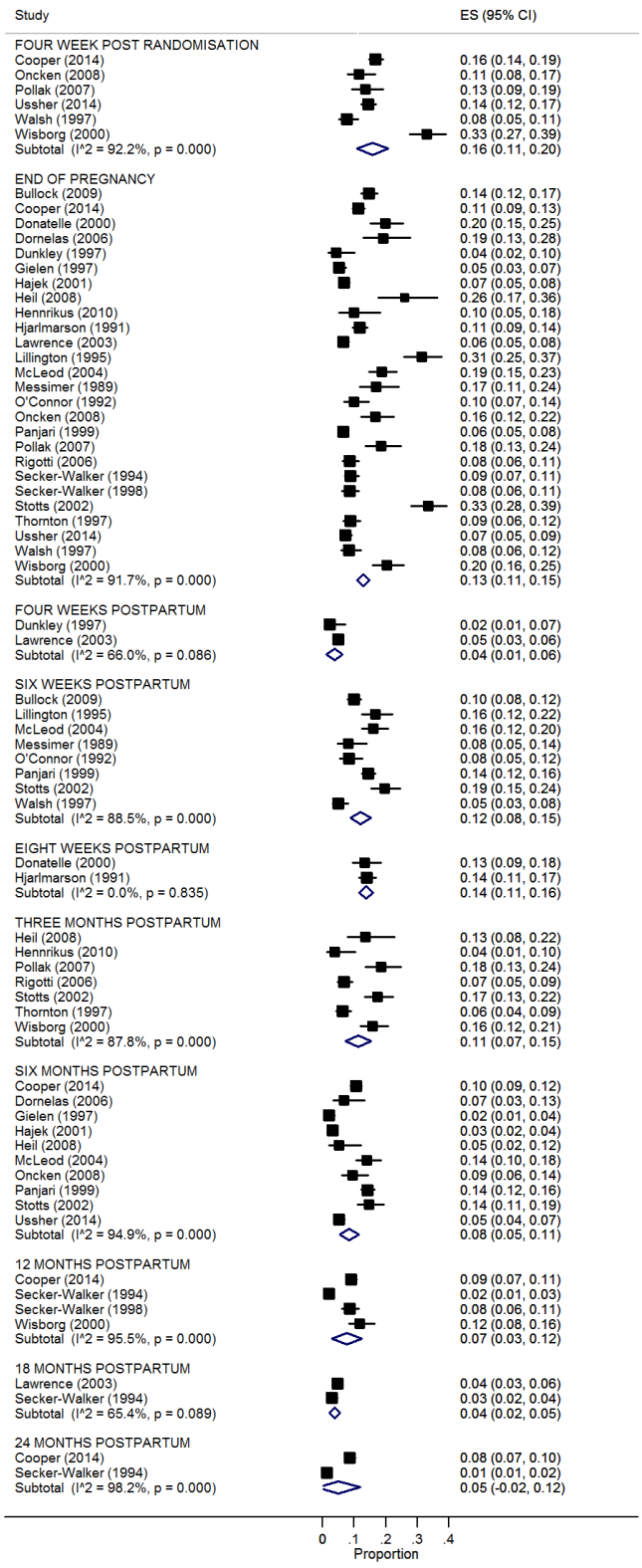


Figure 12.2: Secondary analysis, pooled abstinence using combined data for control participants

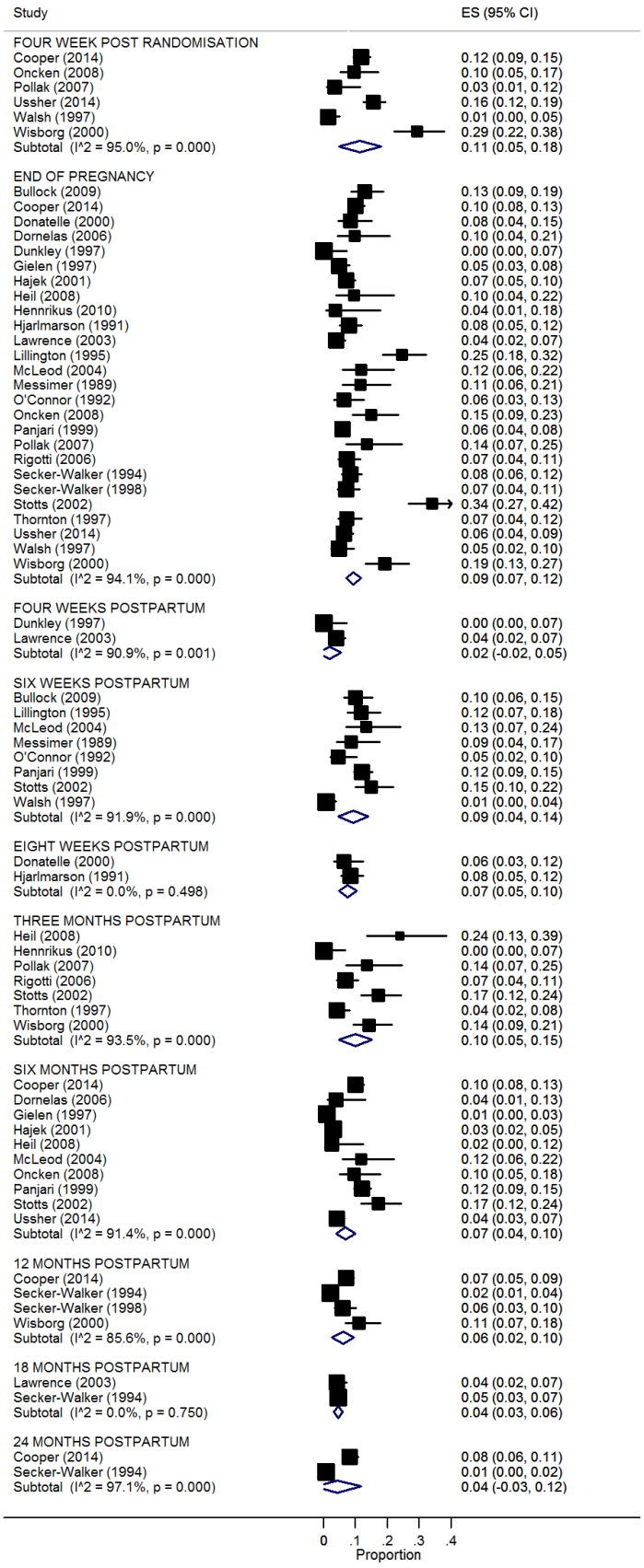


Figure 12.3: Secondary analysis, pooled abstinence using combined data for intervention participants

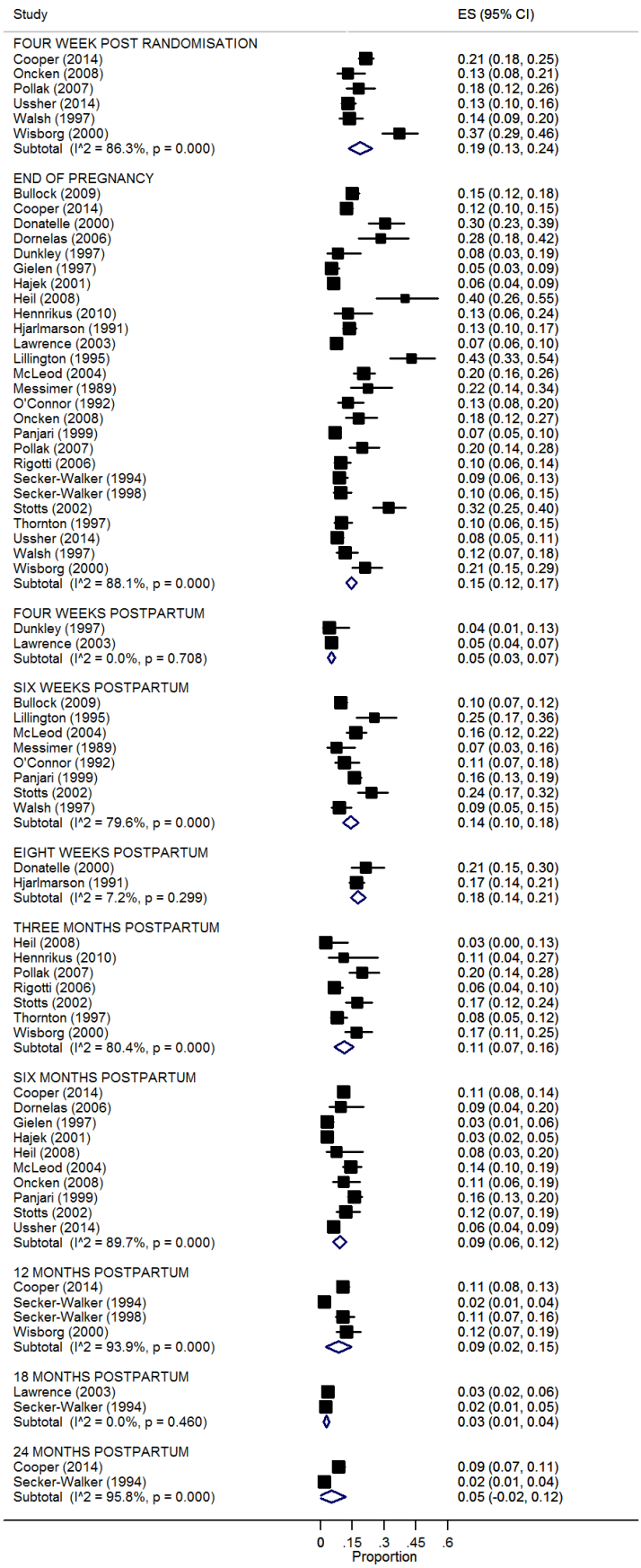
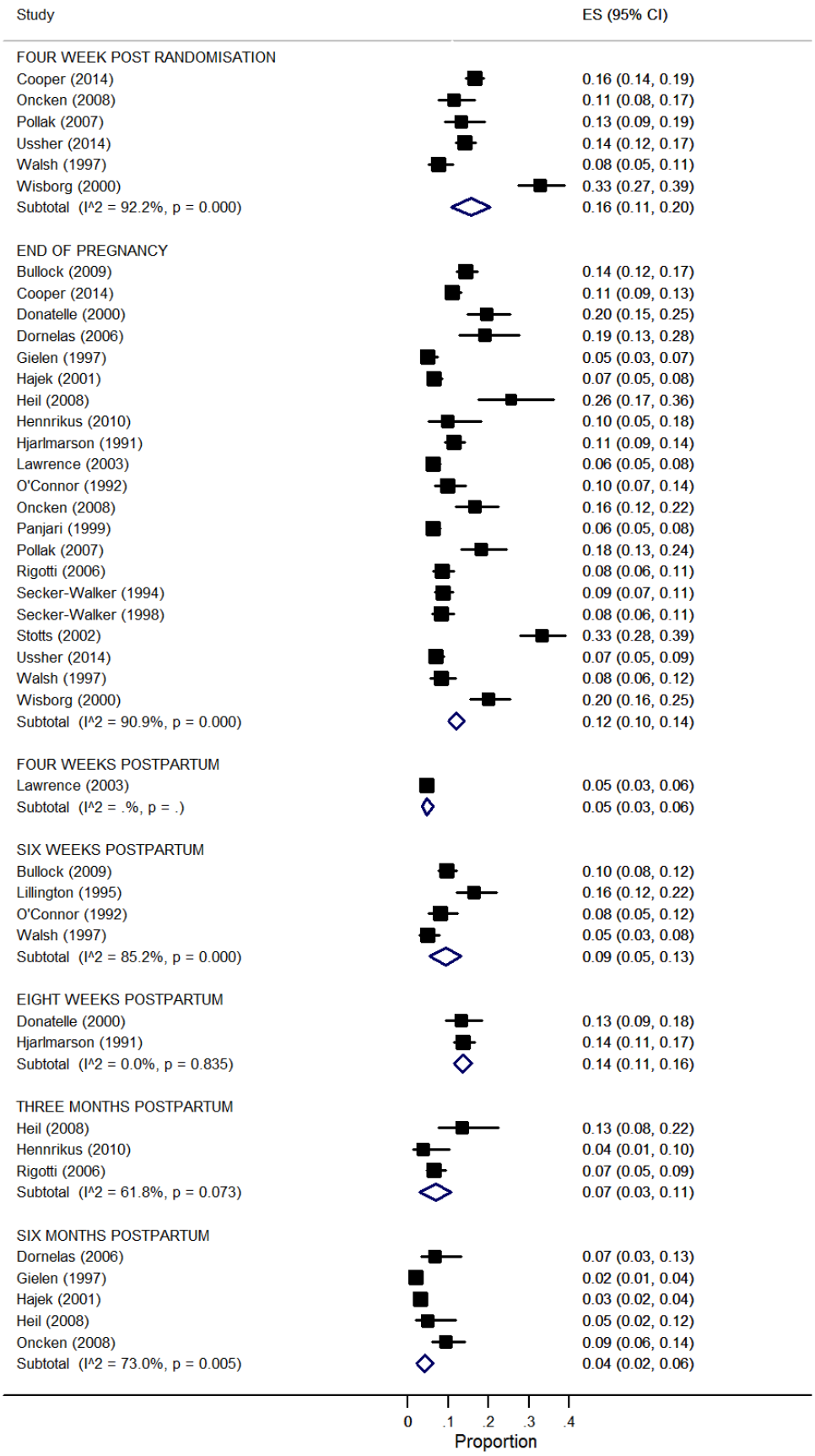


Figure 12.4: Sensitivity analysis, pooled estimates using combined biochemically validated data only



12.7 UK data on the prevalence of smoking related diseases amongst females for use in the Mother's Lifetime Component of the ESIP model.

The prevalence data in this chapter is for all women in the UK, including smokers, former smokers, and never smokers. Due to thesis constraints, calculated smoking contingent prevalences can be found in the ESIP spreadsheet on the "Lifetime disease prevalence" tab.

12.7.1 Coronary heart disease

Table 12.7: Prevalence of CHD by age among women in England, 2006

Age	Prevalence (%)
0-15	0
16-24	0.1
25-34	0.1
35-44	0.3
45-54	1.3
55-64	3.5
65-74	10
75+	19.3
Source: Table 2.13, Compendium of CHD Statistics 2012 **[1126]**	

12.7.2 Chronic obstructive pulmonary disorder

Table 12.8: Prevalence of COPD by age among women in the UK in 2008

Age	Prevalence (%)
0-4	0.01
5-9	0.01
10-14	0.02
15-19	0.03
20-24	0.01
25-29	0.02
30-34	0.04
35-39	0.09
40-44	0.23
45-49	0.53
50-54	1.13
55-59	1.99
60-64	3.14
65-69	4.71
70-74	5.74
75-79	6.81
80-84	6.78
85+	5.30
Source: Chronic disease prevalence by age, sex, SHA, and UK country 2008 **[333]**	

12.7.3 Lung cancer

Table 12.9: Prevalence of LC by age among women in the UK

Age	Prevalence (%)
0-44	0.00
45-64	0.07
65+	0.23
Source: Table 3, Forman et al, EUROPREVAL study **[1127]**	

12.7.4 Stroke

Table 12.10: Prevalence of stroke by age among women in England, 2006

Age	Prevalence (%)
0-15	0
16-24	0.2
25-34	0.1
35-44	0.4
45-54	0.9
55-64	2.3
65-74	4.2
75+	10.7
Source: Table 2.13, Compendium of CHD statistics 2012 **[1126]**	

12.8 Determining the required parameters to fit the Gamma distribution when information on the inter-quartile range was available but not the standard error

The next two pages form the information given to the author to enable the fitting of the Gamma distribution to the NHS Reference costs as these only report the inter-quartile range rather than the standard error. These parameter values were estimated by Professor Murray Smith on behalf of the author as it required the use of Mathematica to which the author did not have access. [1128] The file was sent as a pdf and as such cannot be edited. It is reproduced here as a set of images for information as to how the values were computed.

Gamma Parameter Estimation

Let the random variable X denote cost, and assume it is Gamma distributed with probability density function as follows:

$$f(x;\alpha,\beta) = \frac{x^{\alpha-1}e^{-x/\beta}}{\Gamma(\alpha)\beta^{\alpha}}$$

where $x > 0$ and parameters $\alpha > 0$ and $\beta > 0$. For example, the mean and variance of X are, respectively,

$$E[X] = \alpha\beta$$

and

$$Var(X) = \alpha\beta^2$$

Note too the probability

$$\Pr(X < x) = 1 - \frac{\Gamma(\alpha, x/\beta)}{\Gamma(\alpha)}$$

where the 2-argument $\Gamma(\cdot,\cdot)$ denotes the so-called incomplete Gamma function, having a number of properties, one such being $\Gamma(\alpha, x/\beta) < \Gamma(\alpha)$. Relevant in what is to come is the solution to the inverse probability. To this end there needs to exist a function $H = H(c,r)$ such that the equation $r = \Gamma(c,s)/\Gamma(c)$ can be solved for s; i.e. $s = H(c,r)$. The necessary function does indeed exist and has been hardwired into many softwares, including Excel, as it is the basis for generating pseudorandom drawings from the Gamma distribution. Thus, given a probability p, the inverse probability

$$x = \beta H(\alpha, 1-p).$$

It is worth mentioning here, as it will be needed later, that in the Mathematica programming language $H(c,r)$ is coded: `InverseGammaRegularized[c,r]`.

We have to hand 3 items of sample information on X, being the mean, and the lower and upper quartiles. We transform these into two statistics $(\overline{X}, \overline{R})$, where $\overline{X}$ is the sample mean and $\overline{R}$ the sample interquartile range (upper quartile subtract lower quartile). From these two statistics we wish to estimate α and β using the method of moments estimator. Let a denote the estimator of α and b the estimator of β, then we find (a,b) by solving:

$$\overline{X} = ab$$

and

$$\overline{R} = bH(a,0.25) - bH(a,0.75).$$

Now see that

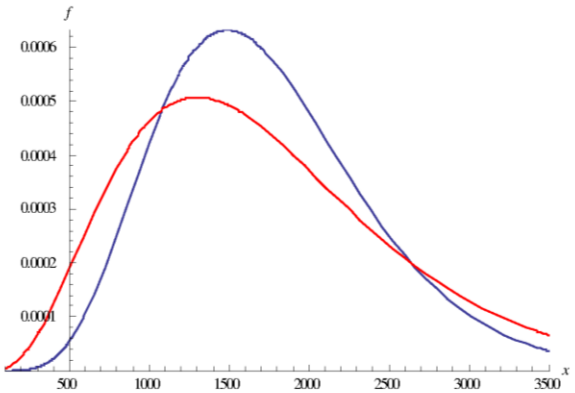
$$\overline{R}/\overline{X} = \frac{H(a,0.25) - H(a,0.75)}{a}$$

eliminates b to yield an equation to be solved for a alone, albeit one that requires iterative numerical methods suited more to formal programming languages. For example, Mathematica can solve this for a with the one-line command:

FindRoot[InverseGammaRegularized[a,0.25] - InverseGammaRegularized[a,0.75] == a r_1, {a, r_2}]

where $r_1 = \overline{R}/\overline{X}$ and $r_2 = \overline{X}^2/\overline{R}^2$ is an initial "guess" for a. Having to hand the solution for a, then obviously $b = \overline{X}/a$.

To illustrate, take the case of ectopic pregnancy for which $\overline{X} = 1749.23$ and $\overline{R} = 2075.46 - 1190.46 = 885$. Then $r_1 = 0.506$ and $r_2 = 3.907$ and Mathematica gives the solution $a = 6.728$ and $b = 260$. The contrast in fitted solution between the methods of moment approach (blue curve) and the estimates given in your spreadsheet (red curve; $a = 3.907$ and $b = 447.761$) are shown here:



Both estimates generate the same mean $\overline{X}$ but the methods of moments fit displays lesser dispersion than your spreadsheet estimates.

Table of estimation results:

Condition	Mean cost	IQR	Gamma a	Gamma b
Treatment for ectopic pregnancy	£1,749.23	£885.01	6.72779	260.001
Treatment for miscarriage	£554.70	£308.94	5.48092	101.206
Community midwife visit	£53.00	£24.00	8.49685	6.23761
Standard ultrasound scan	£109.78	£68.53	4.27769	25.6634
Specialised ultrasound scan	£121.02	£85.22	3.2683	37.0284
Obstetrician first visit	£152.21	£76.10	6.89903	22.0625
Obstetrician subsequent visit	£101.13	£49.40	7.2463	13.9561
Birth (with or withour pre-eclampsia)	£2,079.81	£839.65	10.7905	192.744
Emergency caesarean section birth (abruption)	£3,466.59	£1,164.00	15.7692	219.833
Caesarean section birth (previa)	£3,413.47	£1,164.81	15.2566	223.737
Routine observation (per day)	£571.15	£396.19	3.38171	168.894
Death	£1,379.02	£799.89	5.021	274.65
			Beta a	Beta b
CHD utility	0.73	0.3	2.70794	1.00157

For the CHD utility, a similar procedure to before applies, but this time assume instead a Beta distribution applies. Let the random variable Y denote a utility defined on the unit interval. Assume Y is Beta distributed with probability density function as follows:

$$f(y;\alpha,\beta) = \frac{y^{\alpha-1}(1-y)^{\beta-1}}{Beta(\alpha,\beta)}$$

where $0 < y < 1$ and parameters $\alpha > 0$ and $\beta > 0$. For example, the mean of Y is

$$E[X] = \frac{\alpha}{\alpha+\beta}$$

and

$$\Pr(Y < y) = \frac{Beta(y,\alpha,\beta)}{Beta(\alpha,\beta)}$$

where the 3-argument $Beta(\cdot,\cdot)$ denotes the so-called incomplete Beta function. Relevant in what is to come is the solution to the inverse probability. To this end there needs to exist a function $G = G(r,c,d)$ such that the equation $r = Beta(s,c,d)/Beta(c,d)$ can be solved for s; i.e. $s = G(r,c,d)$. The necessary function does indeed exist and has been hardwired into many softwares. In the Mathematica programming language $G(r,c,d)$ is coded: InverseBetaRegularized[r,c,d]. Thus, given a probability p, the inverse probability

$$y = G(p,\alpha,\beta).$$

We have to hand 3 items of sample information on Y, being the mean, and the lower and upper quartiles. We transform these into two statistics $(\overline{Y},\overline{R})$, where $\overline{X}$ is the sample mean and $\overline{R}$ the sample interquartile range (upper quartile subtract lower quartile). From these two statistics we wish to estimate α and β using the method of moments estimator. Let a denote the estimator of α and b the estimator of β, then we find (a,b) by solving:

$$\overline{X} = \frac{a}{a+b}$$

and

$$\overline{R} = G(0.75,a,b) - G(0.25,a,b).$$

These equations must be jointly solved for a and b. For example, Mathematica can solve this with the one-line command:

FindRoot[{a/(a+b) == $\overline{X}$, InverseBetaRegularized[0.75,a,b] - InverseBetaRegularized[0.25,a,b] == $\overline{R}$}, {a, 0.5}, {b,0.5}]

12.9 **Full size trees illustrating maternal and infant within-pregnancy components**

Figure 12.5: Maternal within-pregnancy component (decision tree)

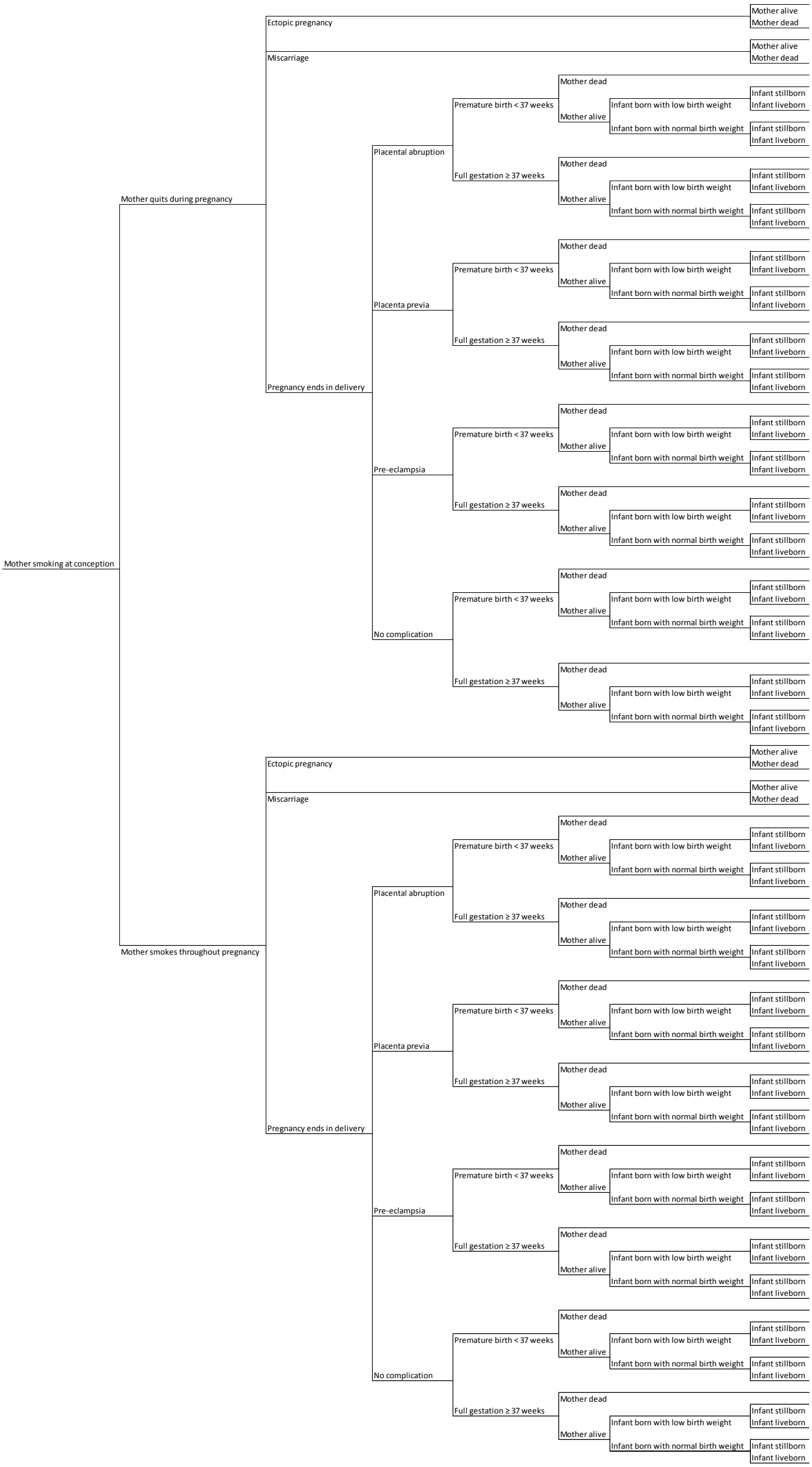


Figure 12.6: Infant within-pregnancy component (decision tree) – part one: mother quits during pregnancy

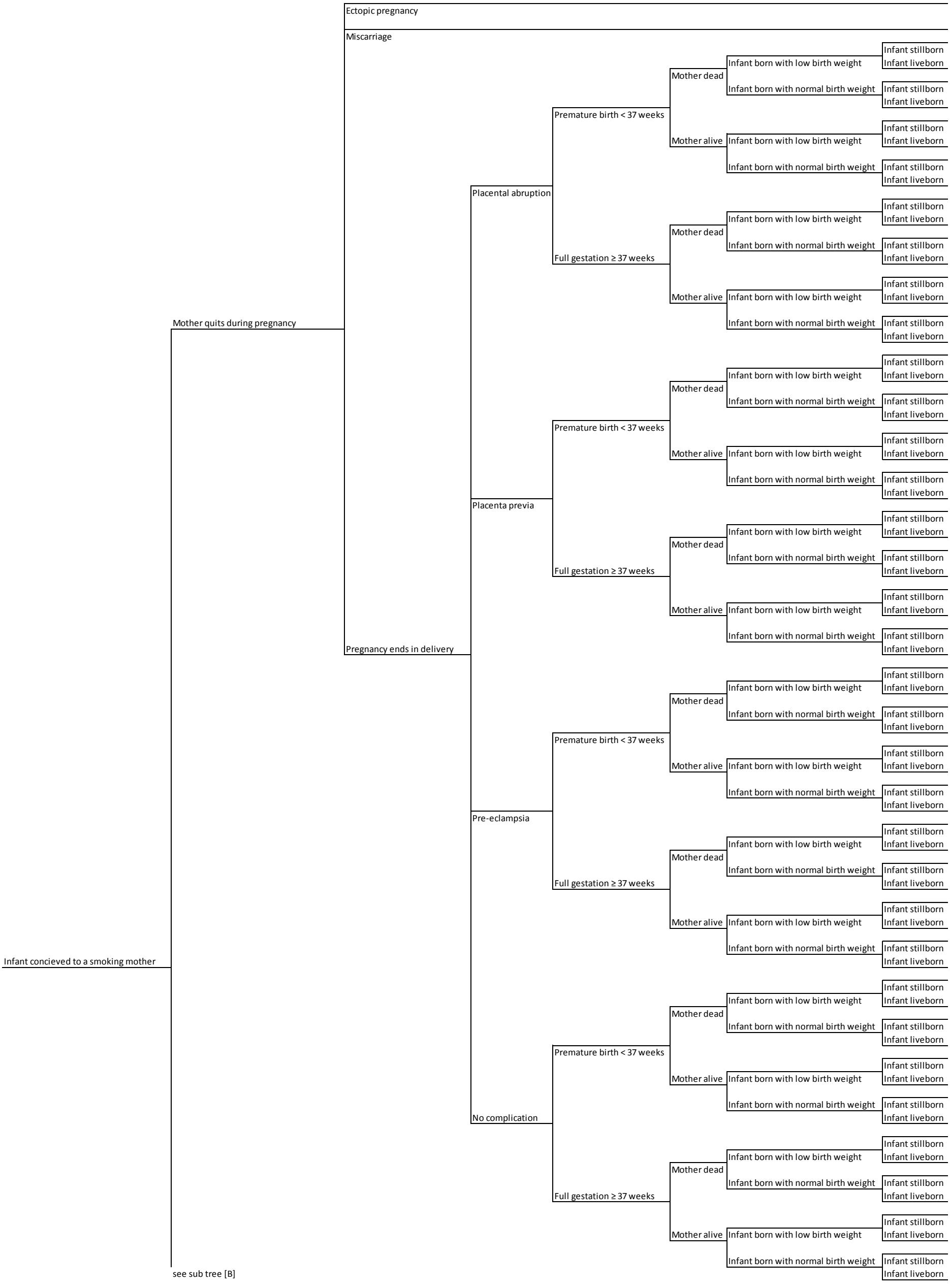
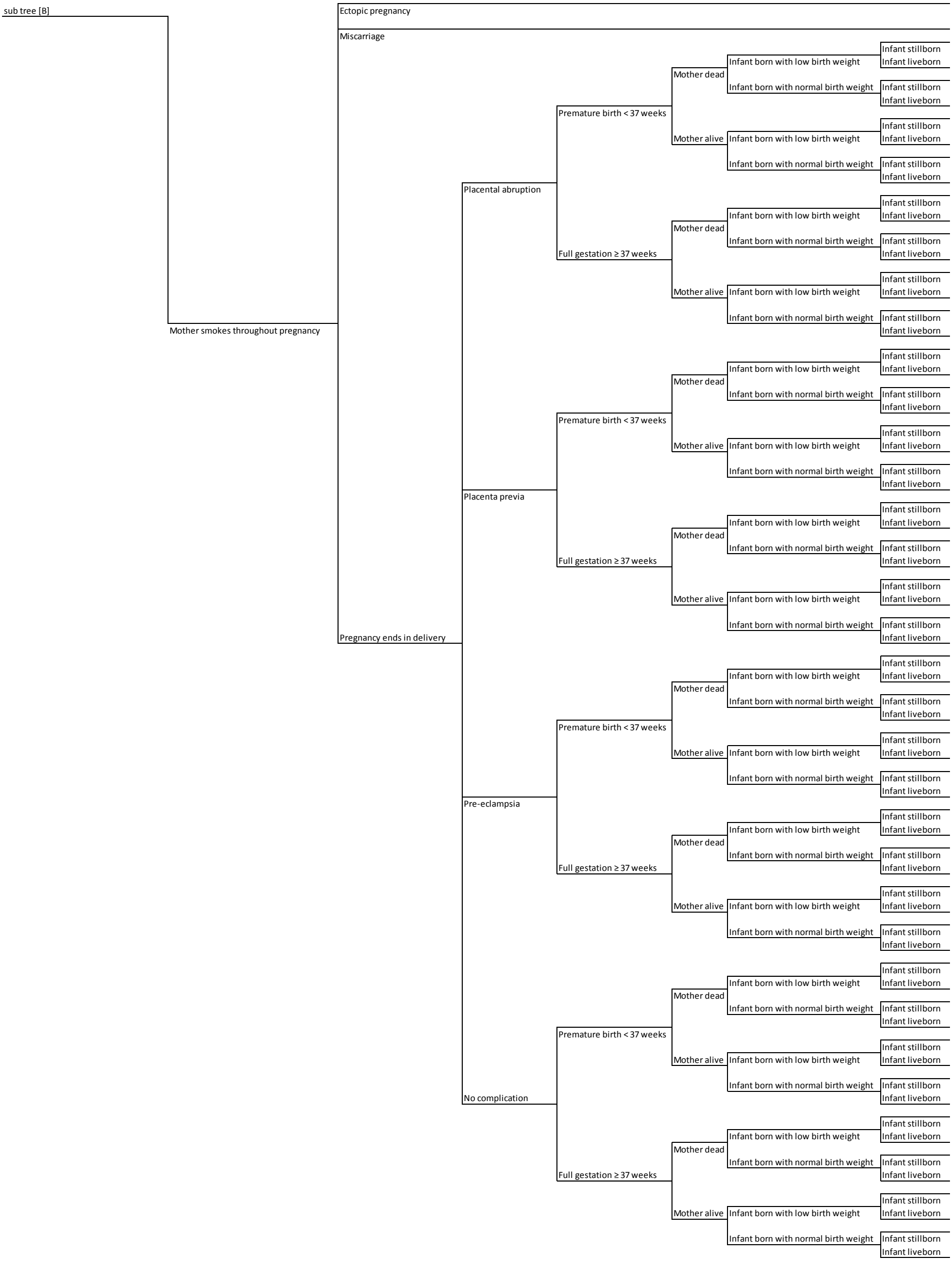


Figure 12.7: Infant within-pregnancy component (decision tree) – part two: mother smokes throughout pregnancy



12.10 **Training and presentations.**

Table 12.11: Masters of public health modules

Code	Module	Semester / Year	Credits
A34587	Epidemiology of Tobacco Use and the Role of the Tobacco Industry	Spring / 2011	15
A34589	Health Economics	Spring / 2011	10
		Total	**25**

Table 12.12: Graduate school short courses

Course name	Course date	Booking reference	Credits
Nature of the doctorate and the supervision process	November 2010	7661	1
Introduction to quantitative research	December 2010	7671	4
Essential information skills for new researchers in medicine and health sciences	December 2010	11217	1
Basic Statistics	December 2010	7673	1
Introduction to Stata for epidemiological analyses (M&HS Faculty)	April 2011	7664	3
		Total	**10**

Table 12.13: External courses

Course name	Course date	Course vendor
Advanced Modelling Methods for Health Economic Evaluation Course	March / April 2011	Centre for Health Economics, University of York
The Nottingham Systematic Review Course	June 2011	Cochrane Schizophrenia Group, University of Nottingham

Table 12.14: Presentations

Conference	Date	Title	Type of presentation
Population Health Methods and Challenges Conference, Birmingham	April 2012	Developing an Economic Model to represent Foetal and Maternal Costs and Benefits of Maternal Smoking Cessation During Pregnancy	Oral

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