ECONOMIC EVALUATION OF SMOKING CESSATION INTERVENTIONS FOR PREGNANT WOMEN

by

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ABSTRACT

Smoking during pregnancy (SDP) is a significant health problem, associated with high healthcare costs and health inequalities. Current SDP interventions are typically cost-effective, but their uptake, content and outcomes are very limited. This thesis aimed to produce evidence to identify the characteristics of 'optimum' SDP interventions, relating to aims (achieving smoke-free households or reducing smoking in the pregnant woman), content (higher financial incentives and more intense behavioural support) and longer duration.

A Markov-based economic model was developed, which extended an existing model by incorporating partners' smoking and the number of cigarettes consumed. A systematic umbrella review informed inclusion of additional health conditions. Three hypothetical interventions were designed based on available evidence, and cost-utility analysis was undertaken to assess their outcomes, healthcare costs and long-term cost-effectiveness compared to standard NHS care. Additionally, a qualitative study in an international public health organisation explored the applicability of high-income country based economic evidence on SDP interventions in low and middle-income countries (LMICs).

The economic modelling found that the hypothetical cessation interventions would greatly extend reach, reduce smoking, address inequalities, and be cost-effective. Piloting of SDP interventions based on this research would be warranted by UK policy-makers, and the findings have potential applicability to LMICs settings.

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Most importantly, I owe a big thank you to my husband, Furkan for his endless encouragement and long chats about my PhD work. Finally, I would like to thank my parents and sisters for always being there for me despite the distance.

"I don't blame people for smoking when I see a social gradient in smoking.

I say we need to understand why it is

the lower you are in the hierarchy the more likely you are to smoke.

So, we need to address the causes of the causes."

Michael Marmot

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
CHD	Chronic heart disease
CEAC	Cost-effectiveness acceptability curve
CE plane	Cost-effectiveness plane
CI	Confidence interval
CO	Carbon monoxide
COM-B	Capability, opportunity, motivation - behaviour
COPD	Chronic obstructive pulmonary disease
CPIT	Smoking Cessation In Pregnancy Incentives Trial
ESIP	Economic impacts of smoking in pregnancy
ESIP.H	Economic impacts of smoking in pregnancy - household
EVPI	Expected value of perfect information
HIC	High-income country
HES	Hospital Episode Statistics
HRG	Healthcare resource groups
ICER	Incremental cost-effectiveness ratio
IFS	Infant Feeding Survey
INB	Incremental net benefit
IPHO	International public health organisation
LBW	Low birth weight
LC	Lung cancer
LIC	Low-income country
LMIC	Low and middle-income country
LYs	Life years
LRI	Lower respiratory infections
MIC	Middle income country
MLC	Mother lifetime component
NHS SSS	National Health Services Stop Smoking Services
NICE	National Institute for Care and Excellence
OAC	Offspring adulthood component
OCC	Offspring childhood component
ONS	Office for National Statistics
OR	Odds ratio
PLC	Partner lifetime component
ppm	Parts per million
PSA	Probabilistic sensitivity analysis
QALYs	Quality adjusted life years
ROI	Return on investment
RR	Relative risk

RSDP	Reduced smoking during pregnancy
SD	Standard deviation
SDP	Smoking during pregnancy
SE	Standard error
SFH3m	Smoke-free household until three months postpartum
SFH12m	Smoke-free household until twelve months postpartum
SID	Sudden infant death
SHS	Second-hand smoking
WHO	World Health Organisation
WPC	Within pregnancy component
WTP	Willingness to pay
UK	United Kingdom

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CHAPTER 1: INTRODUCTION

This PhD work aimed to inform healthcare decision-making by producing better economic evidence to inform the design of smoking cessation interventions for pregnant women. In this chapter, an overview of the dissertation is provided. Firstly, the motivation behind the thesis is explained. Then the objectives and outline are presented alongside a short summary of each chapter.

1.1 Motivation for the Thesis

Smoking is the leading cause of mortality and morbidity, accounting for approximately 79,000 deaths and 1.7 million hospital admissions every year in England (NHS England, 2016). Additionally, smoking is responsible for half of the excess disease among individuals from low socioeconomic backgrounds in England (Jha et al., 2006). Pregnancy is considered a window of opportunity to reduce smoking and thus health inequalities.

Interventions aiming at pregnant women who smoke have particular significance due to the wider effects of smoking during pregnancy (SDP) and the postpartum period, in terms of the impact on infants. Currently, 11% of expectant mothers in England state that they are smoking when asked around delivery time (HSCI, 2019). Additionally, as is the case with the general population, SDP is closely linked to health inequalities since smoking status at the time of delivery is higher in deprived areas of England; for

example it is 27% in Blackpool as opposed to 2% in Westminster (HSCI, 2019). Therefore, smoking cessation interventions aimed at pregnant women can have a positive impact on the health of those at the bottom of the socioeconomic gradient (Marmot and Bell, 2012).

Some attention has been paid to this issue by the UK government especially over the last 20 years (Murray and McNeill, 2012). It has aimed to reduce the proportion of women who smoke at delivery to 6% in England by the end of 2022 (Department of Health, 2017). However, current NHS stop smoking services (SSS) for pregnant smokers are having a limited impact, given that only 22% of pregnant smokers are admitted to NHS SSS (HSCI, 2019). Although some novel interventions exist, they are low-intensity interventions which often end at the point of delivery, resulting in high relapse rates, and other smokers in the household are not considered (Chamberlain et al., 2017). Moreover, there are important limitations to the quality and reliability of the economic evidence on existing SDP interventions (Jones et al., 2015).

Therefore, the motivation behind this PhD work is to produce more accurate economic evidence on SDP interventions for designing better cessation services for expectant mothers, which ultimately would contribute to reducing health inequalities in society.

1.2 Aim and Objectives of the Thesis

The primary aim of this PhD is to develop appropriate methods to identify the characteristics of optimum smoking cessation interventions during pregnancy from a health economic perspective. The objectives are as follows:

- Identifying the health outcomes of smoking during pregnancy and the postpartum period on mothers and infants,
- Building a new economic model for evaluating SDP interventions to generate better evidence for decision makers,
- Investigating how the model can be used to inform the design of hypothetical optimum SDP interventions and
- Assessing how economic evidence produced in high-income countries can inform decision making in low and middle income countries.

1.3 Outline of the Thesis

The thesis starts with background information on SDP in the UK and existing SDP interventions in Chapter 2, including the prevalence and importance of the issue and a discussion on the limitations of current support provided for pregnant smokers. The theoretical foundations, key methods and the use of economic evaluations in healthcare are explained in Chapter 3. This chapter then provides a critical summary of the current economic evaluations of SDP interventions and explains why a new approach is needed.

Chapter 4 presents an umbrella review, also referred to as systematic review of reviews, identifying the health impacts that should be covered in an economic evaluation of SDP interventions. In this chapter, the current evidence on the health outcomes of SDP and the postpartum period on mothers and infants are explored. This

also includes investigating the impact of the number of cigarettes consumed by mothers and that of second-hand smoking by mothers' partners.

Next, the development of an economic model for evaluating SDP interventions is presented in Chapter 5. The chapter provides the sources for model parameters and describes the model structure in detail. The succeeding chapter demonstrates the use of the economic model by evaluating a specific SDP intervention, named MiQuit. The produced model then is used to evaluate different SDP interventions to identify the characteristics of hypothetical optimum cessation interventions conceptualised based on the literature around SDP interventions in Chapter 7. This includes a cost-utility analysis and a return on investment (ROI) analysis.

Since the economic analyses in this thesis are UK-based, the applicability of the findings to other settings warrants attention. Hence, a qualitative study assessing the use of the thesis findings in LMICs is presented in Chapter 8.

In the final chapters, a brief summary of the thesis findings is provided, followed by a discussion on the strength and limitations of the thesis, policy implications of the findings and potential future research.

CHAPTER 2: SMOKING DURING PREGNANCY IN THE UK

2.1 INTRODUCTION

In this chapter, the background information regarding smoking and smoking cessation during pregnancy is presented in two parts. In the first part, the burden of smoking and smoking during pregnancy (SDP) in the UK is presented. In the second part, current stop smoking services available for pregnant women in the UK are discussed. Next, the evidence around cessation interventions for pregnant women is presented. Since financial incentives are the most cost-effective SDP intervention, the next section focuses on the details of the existing interventions involving incentives.

2.1.1 Smoking in the UK

Smoking is a leading cause of preventable deaths and serious health problems (CDC, 2014) and approximately 15% of British adults smoke despite recent decreases in smoking rates (ONS, 2019d). Hence, smoking continues to be a significant public health issue. Figure 2.1 demonstrates how smoking differs across the four countries of the UK (ONS, 2019d). Smoking also relates to health inequalities because people from lower socioeconomic backgrounds are more likely to smoke (ONS, 2019c). For example, a negative correlation exists between education and smoking; 7% of adults

with a degree smoke in England as opposed to 29% in those with no formal education (ONS, 2019d). In line with this, people who carry out manual or routine work are more likely to be smokers, and a similar relationship exists between income and smoking.

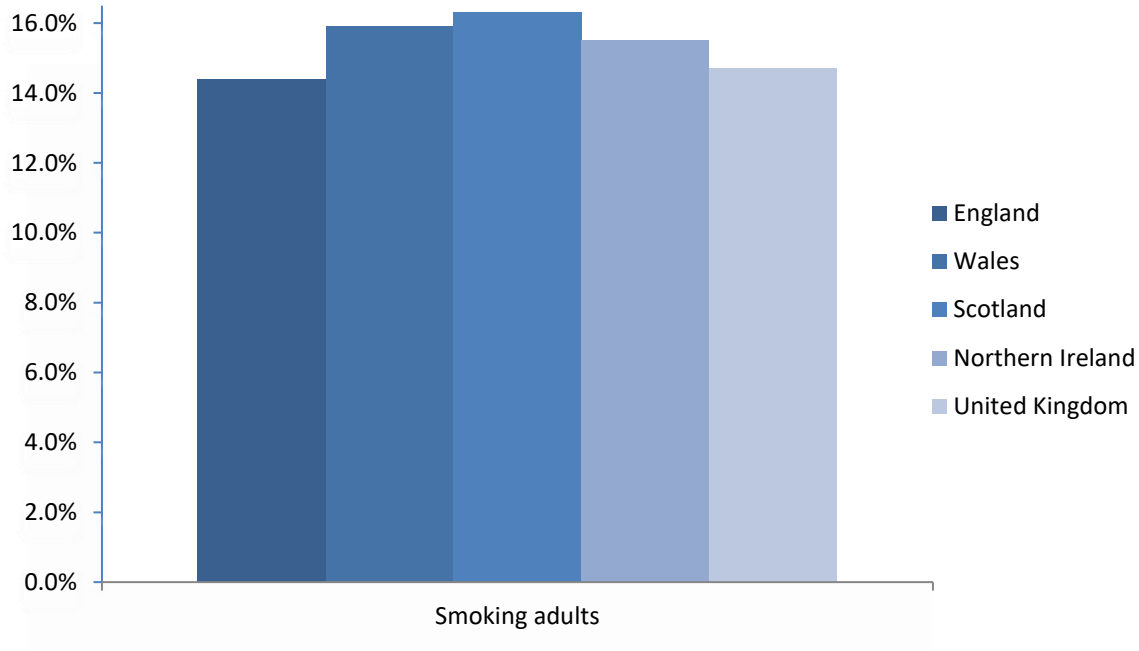


Figure 2.1: Proportion of smoking adults, 2019

Regarding costs, smoking is a considerable burden on society. The total cost of smoking to the NHS is calculated as over £2.6 billion (PHE, 2017). The figure increases to £13 billion when societal costs, such as productivity lost due to premature death, absenteeism and smoking breaks are included (HM Treasury, 2014). Furthermore, prescriptions of smoking cessation products are estimated to cost £28.5 million (NHS, 2017).

Due to the significant health and cost burden, the government in England has set a target to reduce smoking to 12% by 2022, and to 5% in the long-term to create a "smoke-free generation"(Department of Health, 2017).

2.1.2 Smoking during Pregnancy (SDP) in the UK

Self-reported smoking status at delivery is around 11% in the UK (HSCI, 2019). The actual proportion might be higher because evidence indicates a gaming effect whereby 25% of pregnant smokers report quitting by delivery although they continue to smoke (Connor Gorber et al., 2009, Shipton et al., 2009). Hence, SDP affects an important number of women in the UK.

SDP causes several adverse birth outcomes, such as low birth weight (LBW), pre-term deliveries, risk of ectopic pregnancy and stillbirth (Difranza and Lew, 1995, Jauniaux and Greenough, 2007, Lowry and Scammell, 2013, Shah and Bracken, 2000, WHO, 2013). There are also potential long-term health effects on the infant including obesity, diabetes and cognitive development problems (Batstra et al., 2003). Furthermore, there is evidence showing an increased risk of smoking uptake amongst the children of women who smoke while pregnant (Niemela et al., 2016). This, in turn, leads to further health problems linked to smoking.

The disparities in smoking status between the disadvantaged and other members of society are observed among pregnant women as well. In England, for example, the proportion of women smoking during pregnancy is 2% in Westminster as opposed to 27% in Blackpool (HSCI, 2019). The map in Figure 2.2 illustrates the inequalities in SDP across different settings in England. Similarly, in Scotland, the proportion of women who smoked during pregnancy was found to be 30% in deprived areas as opposed to 7% in more affluent areas (Tappin et al., 2010). Therefore, it is clear that SDP is

associated with several socioeconomic factors and people with lower socioeconomic status are more likely to be smoking whilst pregnant.

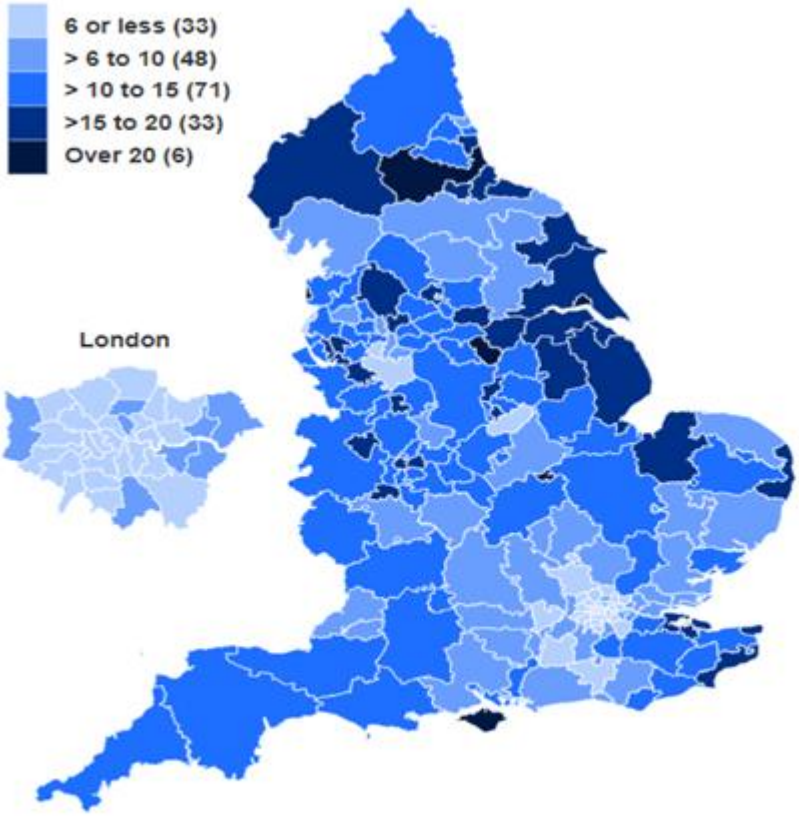


Figure 2.2: SDP prevalence across England

The annual cost of SDP in 2010 was estimated to be between £20 and £87 million (Godfrey et al., 2010). This estimation included maternal health problems (e.g. abortion, ectopic pregnancy) and infant care (0-12 months) due to preterm delivery, LBW, perinatal mortality, sudden infant death (SID), asthma, otitis media and upper and lower respiratory infections (LRI). Therefore, smoking whilst pregnant constitutes

a great burden to individuals and society, especially when the long-term and societal costs are also considered.

2.2 SMOKING CESSATION DURING PREGNANCY

Approximately half of smoking women quit once they realise they are pregnant (IFS, 2010). For the remaining women, however, being pregnant is not a strong enough motivation itself and they need may need some additional support to quit. The World Health Organisation (WHO, (2009a) determines seven groups to target with SDP interventions. These are smokers aged between 15 and 45, early-pregnancy smokers, early-pregnancy quitters, late-pregnancy smokers, pregnancy quitters, continuing smokers and postpartum relapsers. The focus of this PhD project is interventions designed for early-pregnancy smokers who do not quit smoking even after discovering they are pregnant. This section first explains the theoretical background behind smoking cessation interventions aimed at pregnant women and continues with a description of existing stop smoking services in the UK and SDP interventions in the literature.

2.2.1 Theoretical Background of Smoking Cessation during Pregnancy

Smoking is a complex behaviour related to social, psychological and biological factors, and hence tobacco dependence is explained with a biopsychosocial model to refer its trifurcated nature (Engel, 1977, Fernander et al., 2007, Grant et al., 2019). Biological factors include withdrawal symptoms in the absence of smoking, such as anxiety,

depression and increased appetite, whereas psychological aspect covers use of cigarettes as a stress management tool, becoming part of a daily routine. The third part of tobacco dependence relates to social reasons and includes the impact of family, friends and cultural norms. Therefore, smoking is not only a biological addiction but rather it also has psychosocial functions in many women's lives (Morgan et al., 2015).

During pregnancy women often have a strong motivation to quit that is the potential impacts of smoking on the health of the baby. Therefore, pregnancy is often referred to as a *window of opportunity* or a *teachable moment* for smoking cessation with the hope that the women who give up SDP might permanently stop smoking (Cnattingius, 2004, McBride et al., 2003). There is evidence showing a strong association between quitting during pregnancy and remaining abstinent after delivery (Rattan et al., 2013).

However, it is essential to consider personal circumstances and the feelings of the women to understand why some pregnant women do not quit spontaneously. There are a number of health behavioural theories explaining the mechanisms behind smoking cessation (Michie and Prestwich, 2010). A comprehensive review of behaviour change frameworks has resulted with the development of the COM-B model (Michie et al., 2011). The COM-B model offers a strong basis for understanding the barriers which prevent women from responding to the motivation of being pregnant to quit smoking and offers guidance for designing SDP interventions. COM-B focuses on the three functions of behaviour change interventions:

- Capability- physical (e.g. skills) and psychological (e.g. knowledge),
- Opportunity- social (e.g. norms) and environmental (e.g. resources),

- Motivation- automatic (e.g. addiction) and reflection (e.g. beliefs).

Those three are described as the components of the behaviour system. Interventions designed for pregnant women often put more emphasis on the motivation function but focussing on the barriers regarding capability and opportunity could offer more effective support for women (Olander et al., 2016). For example, integrating other smokers at home to generate smoke-free houses might be one way of addressing this (Grant et al., 2019, Morgan et al., 2015).

Interventions that aim to change behaviour are often divided into two categories; policy based interventions, such as tax increase and mass media campaigns, as well as individual level interventions such as education and incentives (Michie et al., 2011). This research project focuses on individual level interventions aimed at pregnant smokers.

2.2.3 NHS Stop Smoking Services for Pregnant Women

NHS stop smoking services (SSS) were established in 1998 following a white paper called “Smoking Kills”, piloted in England during 1999 and implemented across the country in 2000 (Secretary of State for Health, 1998). In 2013, responsibility for SSS were transferred from the NHS to local authorities (Department of Health, 2010). The NHS currently offer a variety of services for people who want to stop smoking, including pregnant women. Those can be categorised at three levels (Dobbie et al., 2015):

- Services delivered by primary care professionals, including brief advice, discussion, awareness raising and referral to SSS,
- Services delivered by community practitioners who have health and social care roles rather than focussing solely on smoking, they provide the above mentioned services in general practitioner (GP) practices and pharmacies,
- Services delivered by smoking cessation specialists who provide behavioural support and work in various locations such as community centres, GP practices and workplaces.

Typically, expectant mothers who smoke are referred to SSS, and the current cessation support available in SSS for these women is limited. Although it is difficult to identify usual practice due to variation between service providers, a recent survey of NHS SSS providers for pregnant women in England reported that all providers offered self-help materials and nicotine replacement therapy (NRT) to pregnant women and that 90% of them provided one-to-one support (Fahy et al., 2014). Based on this survey and some other trial data, usual care in England could be defined as the provision of self-help materials, one face-to-face meeting, the prescription of NRT and one phone call four weeks after setting a quit date (Tappin et al., 2015, Chamberlain et al., 2017). Yet, the most recent UK trial (SNAP trial) shows that NRT has no impact on quit rates amongst expectant mothers (Cooper et al., 2014b). Therefore, the impact of standard care provided for pregnant smokers is potentially very limited.

Additionally, serious concerns have been raised about the reach of SSS since quite a small proportion of smokers who want to quit actually access to those services (Kotz et al., 2009). The number of pregnant women who set a quit date with the NHS SSS was 14,000 although there were around 64,000 pregnant smokers in 2018 (NHS, 2018).

Thus pregnant smokers who are enrolled to the NHS SSS constitute just 22% of all pregnant women who smoke.

Amongst those who engage with the NHS SSS, only 29% quit based on carbon-monoxide (CO) verified rates four weeks after the intervention (HSCI, 2019). Figure 2.3 below demonstrates the number of women who set a quit date with the NHS SSS and quit based on self-reported and CO verified rates at four-week follow-up. There is no data on the long-term abstinence rates amongst those who seek help from the NHS SSS. However, according to trials, 80% of mothers who quit by delivery relapse to smoking by one year after delivery (Ratner et al., 1999). Therefore, there is a need to design effective SDP interventions.

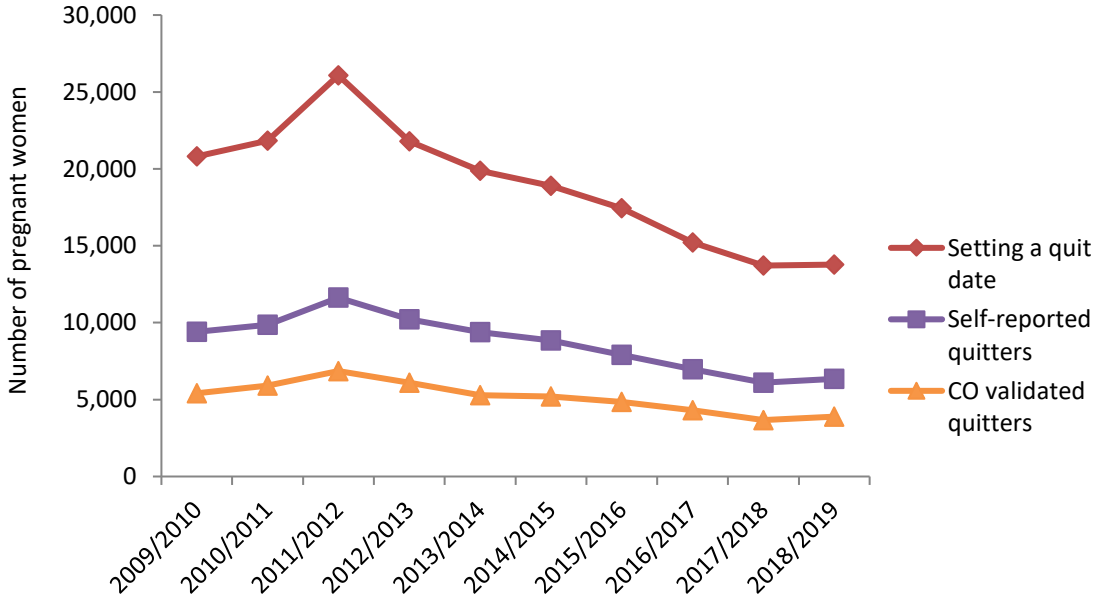


Figure 2.3: Quit rates amongst pregnant women admitted to NHS SSS

Currently, only 31 out of 211 commissioning groups have achieved the target of 6% or less SDP rate (HSCI, 2019). Yet, the spending for SSS has recently declined by around

30% for local authorities due to national austerity policies (ASH, 2019). Thus, the cost-effectiveness of SDP interventions is an important consideration.

2.3 SMOKING CESSATION INTERVENTIONS FOR PREGNANT WOMEN

There are different types of interventions aiming to increase smoking cessation rates among childbearing women which could be divided in two main groups; pharmacological and psychosocial interventions (Chamberlain et al., 2017). The pharmacological interventions mainly consist of Nicotine Replacement Therapy (NRT) (Cahill et al., 2013). NRT can be in the form of patches, gum, tables, lozenges, nasal spray, and inhalators. Additionally, e-cigarettes could be viewed as pharmacological aids. The most commonly used psychosocial interventions are cognitive behaviour strategies, counselling, feedback, physical activity and rewards (Ussher et al., 2015, Taylor, 2009, Mallender et al., 2013).

2.3.1 Pharmacological Interventions

Pharmacological interventions aim to reduce the symptoms caused by withdrawal by providing a certain amount of nicotine. The following conditions must be satisfied before prescribing any NRT treatment for pregnant women (WHO, 2001):

1. Patient received “Best Practice” (e.g., SCRIPT) and did not quit.
2. Patient smokes 10 or more cigarettes daily.
3. Patient smokes during the first 60 minutes after waking up.

4. Patient has the willingness to quit.
5. Gestational age is less than 20 weeks.

In parallel with the advice from WHO, National Institute for Care and Excellence (NICE) recommends that NRT should not be offered, unless other cessation methods have failed to help women to quit (NICE, 2010). No other type of pharmacotherapy is advised for pregnant or breastfeeding women.

Regarding the effectiveness of pharmacotherapy during pregnancy, a recent meta-analysis showed that the quit rate by delivery was higher amongst those who received NRT than in non-placebo controls (RR=8.51, 95% CI, 2.05-35.28). Nevertheless, the difference was not significant if only robust studies with placebo controls were considered (RR=1.28, 95% CI, 0.99-1.66) (Coleman et al., 2015). There was no significant impact on birth outcomes, but the women reported some side effects, such as, headaches, nausea, and local reactions. Likewise, a recent trial found that NRT helped women to quit over a one month period but at delivery time, NRT did not show any difference compared with placebo (Cooper et al., 2014b). Therefore, based on the available evidence, NRT has very limited impact on cessation among pregnant women.

In addition, e-cigarettes warrant consideration since they are used by many to quit smoking. Offering e-cigarettes to those who smoke during pregnancy is not recommended as standard care in the UK. More generally, however, the NHS regards e-cigarettes to be a cessation aid since they are less harmful than SDP (NHS, 2016). E-cigarettes include 95% less harmful ingredients than conventional cigarettes (McNeill et al., 2018). Yet, there is no evidence on the effectiveness of e-cigarettes amongst

pregnant women although there are some studies showing some important benefits of e-cigarettes in the general population (Malas et al., 2016).

2.3.2 Psychosocial Interventions

Psychosocial interventions aim to provide behavioural support for pregnant women who smoke. They include a wide range of psychological and social components to encourage women to stop smoking and prevent them from relapsing. The most commonly used approaches are providing self-help materials, using cognitive behaviour strategies, providing counselling, giving feedback based on biochemical measurements, encouraging physical activity and issuing rewards (mostly financial incentives) (Ussher et al., 2015, Taylor, 2009, Mallender et al., 2013). They can be provided alone or in combination with pharmacotherapy.

Regarding the effectiveness of psychosocial interventions, Chamberlain et al. (2017) reviewed SDP interventions aimed at pregnant women. They reported that counselling (RR=1.44, 95% CI 1.19-1.73), feedback (RR=10.21, 95% CI 1.89-10.21) and incentives (RR=2.36, 95% CI 1.36-4.09) increased quit rates in late pregnancy while the impacts of health education (RR=1.59, 95% CI 0.99-2.55) and social support (RR=1.42, 95% CI 0.98-2.07) remained unclear. Effectiveness varied based on the characteristics of the interventions; for example, the inclusion of self-help materials and telephone support increased the effect size.

Financial incentives were found to provide the greatest effectiveness regarding quit rates across all psychosocial smoking cessation interventions in this review

(Chamberlain et al., 2017). Cahill et al. (2015) conducted another Cochrane review which included nine trials involving financial incentives for pregnant women and the results were favourable (RR=3.60, 95% CI 2.39-5.43).

Regarding abstinence after delivery, interventions were found to increase the number of women who were abstinent between delivery and five months postpartum compared to usual care, with financial incentives providing the greatest impact (RR=3.63, 95% CI 1.54-8.58) (Chamberlain et al., 2017). Nevertheless, relapse rates among those who quit have remained considerably high. A systematic review identifying postpartum relapse rates amongst women who received SDP interventions reported that by six weeks postpartum, 43% of those who had quit started to smoke again (Jones et al. 2016). The relapse rate at 12 months postpartum among those who had quit at delivery was 47%, and 80% according to the bio-chemically verified results (Jones et al. 2016, Ratner et al. 1999). Hence, the long-term impact of existing SDP interventions was very limited.

2.3.3 Financial Incentives

As noted above, the evidence suggests that financial incentives are the most effective intervention for smoking cessation in pregnancy. Hence, in this section, interventions involving financial incentives are investigated in detail. Two reviews have identified several studies focussing on the effectiveness of financial incentives during pregnancy (Cahill et al., 2015, Morgan et al., 2015). The target population of the interventions included in those reviews were similar. However, their characteristics varied in terms

of intervention design, comparator, outcome measurement and the consideration of relapse rates.

2.3.3.1 Population

All interventions included in the reviews recruited pregnant mothers who smoked and wanted to quit, and the participant selection criteria were similar. Some included women whose CO levels were 7 ppm or more (Ierfino et al., 2015, Tappin et al., 2015) while in one study (Cooper et al., 2014b) the required CO level was defined as at least 8 ppm for eligibility. Another eligibility criterion was gestation week which was mostly identified as early pregnancy, such as 10 to 24 weeks (Ussher et al., 2015), 12 to 24 weeks (Cooper et al., 2014b) and less than 30 weeks (Tuten et al., 2012). Hence, the target population was comparable across studies.

2.3.3.2 Intervention

There are certain characteristics that can be used to classify financial incentives interventions as shown in Figure 2.4 below. This classification has been developed based on the two reviews and six studies published after the reviews (Ierfino et al., 2015, Lopez et al., 2015, Ormston et al., 2015, Radley et al., 2015, Tappin et al., 2015, Ussher et al., 2015, Cahill et al., 2015, Morgan et al., 2015), monetary rewards ranging from high value of vouchers (Heil et al., 2008, Higgins et al., 2014, Tuten et al., 2012) to inclusion into a lottery (Ussher et al., 2015).

Financial incentives can be provided contingent to a behavioural change or without any conditions. Incentives could be supplied for different achievements, such as

quitting smoking, reducing the amount consumed or both. For example, in one intervention, incentives were provided if the women quit smoking and remained abstinent until delivery (Tappin et al., 2015), whereas in another study, women were eligible for financial rewards for both reduction and quitting (Tuten et al., 2012). In most of the studies, smoking was defined as a binary condition, focussing on quitting only. However, a reduction in the number of cigarettes could be considered as a condition of financial incentives, due to the positive health impacts on the mother and foetus (Ko et al. 2014, Niemela et al. 2016).

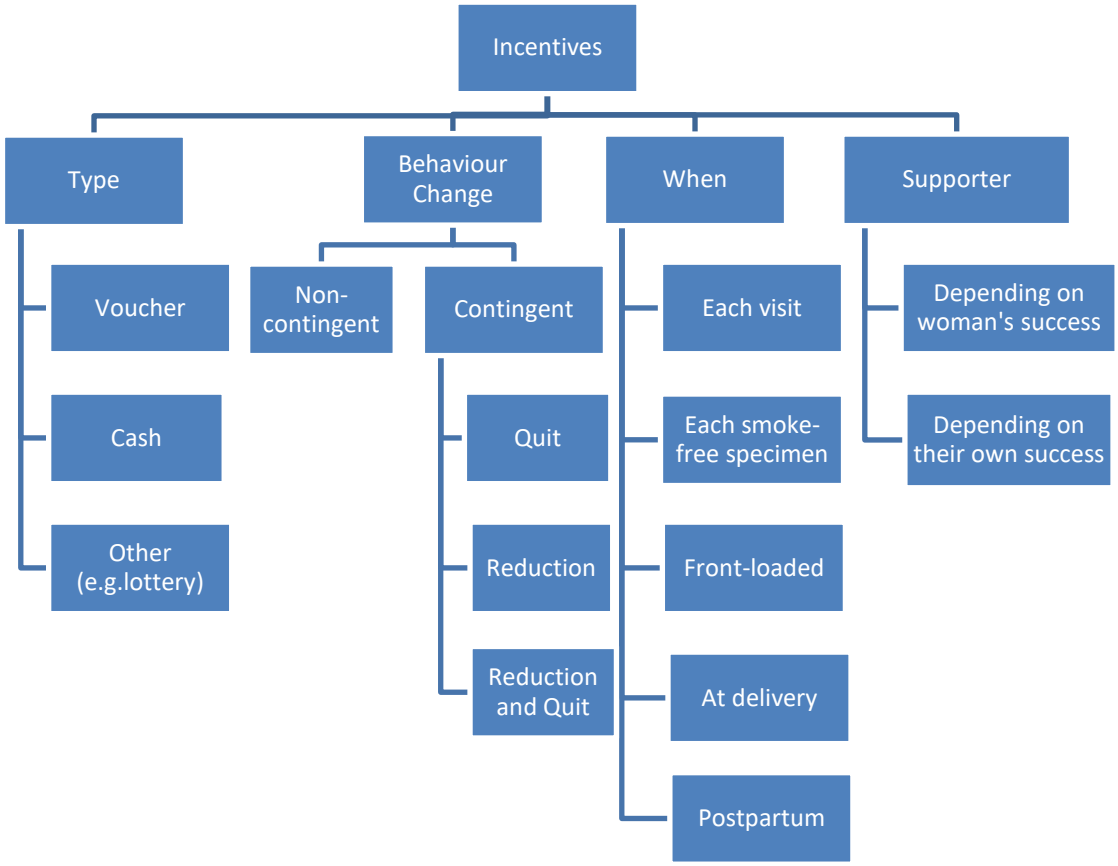


Figure 2.4: Types of financial incentives

Additionally, the time point when financial incentives were issued differed across interventions. Women were provided with the incentives for each visit (Donatelle et al., 2000), each smoke free specimen (Heil et al., 2008, Jon Dawson Associates Ltd, 2014, Tappin et al., 2015, Tuten et al., 2012), for abstinence at delivery or after delivery (Ierfino et al., 2015, Radley et al., 2015).

Inclusion of a supporter who is often a family member or a friend is considered an effective strategy to help women quit, as women who smoke during pregnancy have emphasised that it is important (Morgan et al., 2015). Therefore, in one intervention the supporter was incentivised contingent on the woman's abstinence (Donatelle et al., 2000), which increased quit rates at delivery.

Furthermore, pregnancy could be an opportunity to change the behaviours of other family members to generate smoke-free houses. There is evidence showing that partners of smoking pregnant women can quit while supporting these women to quit (Aveyard et al., 2005, Hemsing et al., 2012). However, there is a paucity of evidence regarding the effectiveness of providing financial incentives to a supporter contingent on their own abstinence.

2.3.3.3 Comparator

The interventions were conducted in different settings, and hence comparators differed across studies. For example, both Tappin et al. (2015) and Ussher et al. (2015) used NHS standard care as the comparator. Nevertheless, it was defined as specialist pregnancy support by SSS in the former, which included one-hour face-to-face advice,

four weekly phone calls and NRT for 10 weeks. In contrast, the latter study determined standard care as behavioural support delivered via a two-day course and six-weekly sessions. Therefore, it is important to consider details of the comparator while assessing the effectiveness of a financial incentive intervention.

2.3.3.4 Outcome

The main study outcome was quitting smoking, namely abstinence, in all interventions except one which also considered reducing smoking (Tuten et al., 2012). However, there were variations in the definitions of abstinence and the measurements used across studies.

2.3.3.4.1 Defining abstinence

There are different definitions of abstinence applied in the literature as summarised by Hughes et al. (2003). Continuous abstinence captures uninterrupted abstinence between the quit date and follow-up, prolonged abstinence refers to abstinence after an initial grace period. Point prevalence abstinence means the prevalence of abstinence during a time window just before follow-up and repeated point prevalence measures abstinence at two or more follow-ups and smoking is allowed between those points. These definitions are illustrated in Figure 2.5.

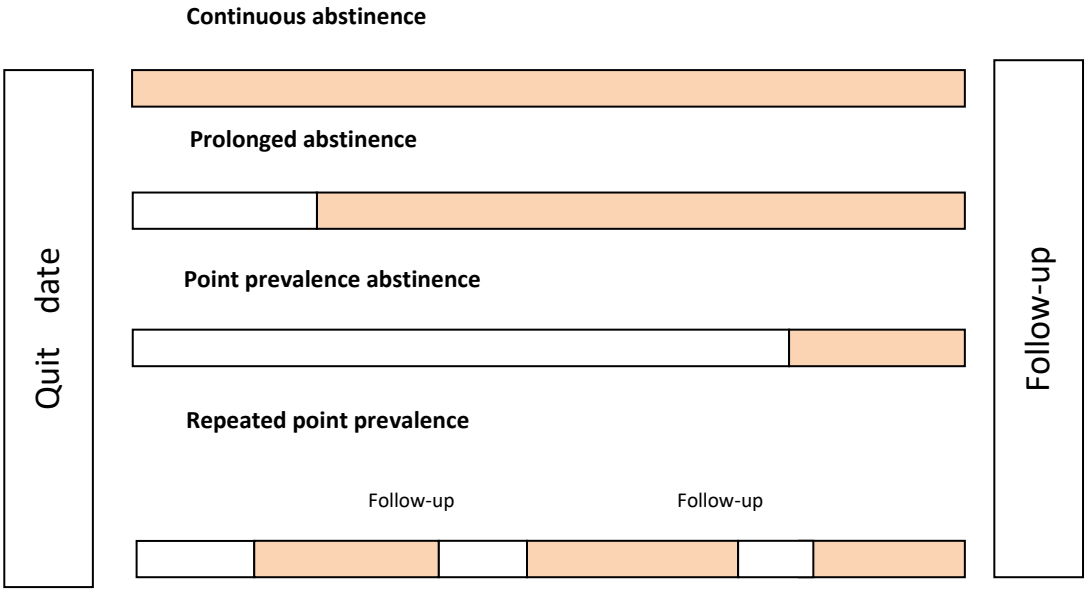


Figure 2.5: Definition of abstinence (Adopted from Hughes et al. (2003)

Continuous abstinence is generally criticised in the literature as there is no grace period when some subjects might smoke a small number of cigarettes but then quit afterwards (Hughes et al., 2003). That causes those who smoke in the beginning but then do not smoke later on to be counted as having relapsed although some might eventually quit smoking altogether. Point prevalence abstinence can take this into account because of the grace period. However, point prevalence often involves a very small time period to fulfil a criterion of abstinence, and includes people who remain abstinent for different periods, ranging from one week to many months. Having a primary end-point is thought to balance the two extremes of point prevalence abstinence and continuous abstinence measures because the former causes overestimation, whereas the latter underestimates the number of people who are

abstinent (West et al., 2005). Specifically, repeated point prevalence measurements are suggested as optimal because it is difficult for a smoker to be abstinent at regular follow-ups and smoke in between (Hughes et al., 2003). Moreover, a systematic review showed that prolonged abstinence and point prevalence abstinence produce similar results in the general population (Hughes et al., 2010).

The studies investigating the effectiveness of financial incentives mostly utilised point prevalence measurement but some measured more than one type of abstinence as a response to the aforementioned limitations (Chamberlain et al., 2017, Morgan et al., 2015). Hence, the results of the reviewed studies were comparable.

2.3.3.4.2 Verifying abstinence

Smoking abstinence can be measured via self-reporting or biochemical verification. Although it is widely used, self-reported measurement has a high risk of bias. Especially if there is a reward contingent on abstinence, trial participants might report their smoking status incorrectly (Ierfino et al., 2015). Therefore, biochemical verification is required to measure abstinence correctly. Currently, biochemical verification of smoking status is often examined by measuring CO and cotinine levels via breath, salivary and urine tests. There is a widely used standard for defining abstinence from smoking called the Russell Standard (West et al., 2005). This defines abstinence as self-reporting having smoked less than five cigarettes since the abstinence period started, confirmed by biochemical verification.

Regarding biochemical verification, there is a great diversity in the literature, with thresholds ranging between 10ng/ml and 25ng/ml for saliva and 50ng/ml and 200ng/ml for urine cotinine levels (Kim, 2016). The widely accepted thresholds in the general population are 15ng/ml for saliva or 50ng/ml for urine (Jarvis et al., 2003). However, evidence shows that cotinine levels in smoking women differ during and after pregnancy (Rebagliato et al., 1998). A study looking at the thresholds for pregnant and newly postpartum women found that 80ng/ml could be used for urine testing and 4ppm for breath testing although cut-off levels for salivary testing was not investigated (Higgins et al., 2007). Therefore, the standards for biochemical verification of abstinence in pregnant women are not well-established.

There was also variation in relation to the cut-off levels of abstinence in the interventions with financial incentives. For example, Tappin et al. (2015) defined the cut-off levels as salivary cotinine less than 14.2ng/ml and urine cotinine less than 44.7ng/ml. In another study, however, the figure for a urine cotinine test was 80ng/ml (Higgins et al., 2014). Moreover, in one study the threshold for urine cotinine was defined as 200ng/ml without any justification (Donatelle et al., 2000). Regarding breath tests, Tuten and others (2012) used a cut off level of 4ppm, whereas it was accepted as 6ppm in another study (Heil et al., 2008). There was often no justification for the choice of the cut-off levels. Therefore, the impact of measurement methods on study results was not clear.

2.3.3.4.3 Quit rates

All studies in the reviews reported quit rates at delivery (Cahill et al., 2015, Morgan et al., 2015). Better outcomes have been achieved with the contingent financial incentives (Higgins et al., 2014, Tuten et al., 2012, Morgan et al., 2015). A meta-analysis of four studies comparing contingent incentives with non-contingent incentives found that the women provided with contingent incentives were 2.58 times (95% CI, 1.63-4.07) more likely to quit towards the end of pregnancy (Morgan et al., 2015). Issuing most of the rewards during the first weeks of the intervention (front-loaded incentives) had a similar effect although this was not statistically significant (Higgins et al., 2014). Hence the impact of timing is not clear in the evidence to date.

2.3.3.4.4 Reduction and quit attempts

Although smoking is often considered a binary condition, the number of cigarettes consumed is an important consideration. There is evidence showing that the risk of experiencing many health conditions increases as the number of cigarettes consumed rises. Hence, there are health benefits of a reduction in SDP, and those who reduce smoking are more likely to quit in the future (Begh et al., 2015).

Similarly, those who have tried quitting before are more likely to succeed in their following attempts. Thus, reduction and quit attempts can be viewed one of the key outcomes of cessation interventions. Only one financial incentives study has reported on the reduction in the number of cigarettes consumed (Tuten et al., 2012). Additionally, some studies reported quit attempts in addition to quit rates (Ormston et al., 2015, Radley et al., 2013, Radley et al., 2015).

2.3.3.4.5 Relapse rates

Studies with financial incentive studies aimed at pregnant women have frequently looked solely at the short-term effects and have not investigated long-term outcomes. Studies have utilised different follow-up points, which were between three months (Radley et al., 2013) and six months postpartum (Tappin et al., 2015). The relapse rate in the study with the longest follow-up was 65% in the intervention group as opposed to 81% in the control (Tappin et al., 2015).

According to available evidence, financial incentives reduce the relapse rates in pregnant women at six months postpartum. Nonetheless, the measurement at follow-up was often self-reported abstinence (Tappin et al., 2015, Tuten et al., 2012) or CO breath test (Ierfino et al., 2015, Ormston et al., 2015, Radley et al., 2013) which is a less reliable measure compared to salivary or urine cotinine tests. Therefore, the actual relapse rates are likely to be greater than those reported in the studies. Furthermore, there is a lack of evidence on the impact of financial incentives on abstinence beyond six months postpartum.

2.3.4 Financial Incentives in Combination with Social Support

Since financial incentives are the most effective and cost-effective SDP intervention and social support is an important component of behavioural change, it is important to understand whether their impact is increased when provided in combination.

The systematic review by Chamberlain et al. (2017) reported 16 interventions measuring the impact of social support. All but one of the interventions included an individual within the network of the women but not necessarily living at the same household. One study (McBride et al., 2004) incorporated partners to support women as well as to help partners who smoke quit. The intervention showed a 4% increase in quit rates amongst women at two months postpartum although it was not statistically significant (p=0.025). Additionally, it lengthened the abstinence duration for women (246 versus 357 days between delivery and relapse) and increased quit rates in partners. Yet, it included only six phone calls in addition to the usual care which was one face-to-face meeting and self-help material. Thus, a more intensive and longer-term intervention might provide a greater impact considering the effect of partner behaviour on SDP (Morgan et al., 2015).

The review by Chamberlain et al (2017) found three studies investigating the impact of financial incentives in the form of a lottery draw (Lillington et al., 1995, Walsh et al., 1997) and vouchers in combination with a supporter (Donatelle et al., 2000); all reported significant increases in quit rates at delivery and six months postpartum. However, only the study by Donatelle et al. (2000) allowed supporters to earn vouchers as well as the women. Women who stayed abstinent and their supporters won vouchers worth $50 each per month for the first and last months and $25 per month in between until two months postpartum. Women in the experimental group were more likely to be abstinent than those in the control group at eight weeks gestation (RR= 3.64 95% CI 1.84, 7.23). However, the intervention did not have any

impact on the probability of abstinence among those who had quit at the time of delivery.

It should be noted that Donatelle et al. (2000:1) identified the supporter as "*preferably a female non-smoker with whom the participant had a regular, close, positive association".* Thus, incorporating partners who smoke instead of non-smoking supporters might increase the effectiveness of such interventions and reduce relapse rates, considering the impact of partners' smoking on pregnant women (Kia et al., 2018, Morgan et al., 2015, Prady et al., 2012, Ratner et al., 1999).

2.3.5 Smoke-free Household Approach and Financial Incentives

The review of the evidence suggests that there is no SDP intervention that combined a smoke-free household approach with financial incentives (Chamberlain et al., 2017).

The impacts of second-hand smoking (SHS) during pregnancy and the postpartum period on mothers and infants are profound (Salmasi et al., 2010). Additionally, women who smoke are less likely to quit before or during pregnancy if their partners smoke, compared to women with non-smoking partners, and those with partners who quit smoking (Fitzpatrick et al., 2016, Morgan et al., 2015).

Moreover, relapse rates by nine months postpartum are considerably lower among women whose partners quit during pregnancy and remained abstinent (Prady et al., 2012). Thus, a household approach is necessary in smoking cessation interventions targeting pregnant women. NICE (2010) also recommends having a household

approach to help pregnant smokers by incorporating their partners through multiple contacts.

2.3.6 Interventions Targeting Women Not Committed to Quit

SDP interventions typically have targeted women who wanted to quit and included only those who were ready to quit (Chamberlain et al., 2017), which explains the high quit rates among trial participants (9%) estimated by Jones (2015) compared to the spontaneous quit rate among pregnant smokers in England (2%). A potential way to include those who are not committed to quit is to offer help with reducing the number of cigarettes consumed.

Only six interventions reported by Chamberlain et al. (2017) demonstrated a statistically significant improvement in increasing the number of women who reduced the amount of daily cigarette consumption (Cook et al., 1995, Price et al., 1991, Tuten et al., 2012, Valbös and Nylander, 2019, Windsor et al., 1993, Windsor et al., 2014), of which two did not provide a clear definition of reduction (Price et al., 1991, Valbös and Nylander, 2019) and one was published as an abstract which did not contain the intervention details (Cook et al., 1995).

The trial by Windsor et al. (2014) consisted of self-help materials, one face-to-face counselling session, and encouragement of a smoke-free house policy and partner support. 11% of participants reduced smoking (50% or more) during late pregnancy in the intervention group compared to 7% in the control ($p=0.05$). Additionally, 34% of households were smoke-free in the intervention compared to 32% in the control

(p=0.709). The intervention by Tuten et al. (2012) reported that 48% of women in the intervention group which received financial incentives achieved the 75% reduction target in carbon monoxide (CO) levels against none in the control group. Hence, there is some evidence showing that behavioural support, a smoke-free household approach and financial incentives could help pregnant smokers reduce the number of cigarettes consumed.

2.4 CONCLUSION

Smoking during pregnancy is an important public health issue in the UK due to the adverse health impacts and health inequalities. The reach and impact of current NHS Stop Smoking Services for pregnant women are limited. The evidence suggests that long-term interventions with financial incentives are the most effective and cost-effective way of supporting expectant mothers to quit. Yet, the existing interventions are short-term and relapse rates are high. Additionally, there is limited evidence on the effective interventions to support women who are not yet ready to quit entirely.

To achieve the government's target of 6% SDP by the end of 2022, novel cessation interventions are required. Despite the evidence showing the effectiveness and cost-effectiveness of SDP interventions, funding for those services is strained. Therefore, there is a need to analyse which interventions could produce the greatest impact, taking into account their cost-effectiveness.

CHAPTER 3: ECONOMIC EVALUATIONS IN HEALTHCARE

3.1 INTRODUCTION

In this chapter, the background information regarding economic evaluations in healthcare is provided. The chapter starts with the theoretical foundations of economic evaluations and their role in healthcare. In the succeeding section, the process of undertaking economic evaluations is explained, followed by the description of different types of economic evaluations. Next, the limitations of existing economic evaluation approaches are discussed. Finally, the last section focuses on the economic evaluation of SDP interventions.

3.1.1 The Importance of Economic Evaluations in Healthcare

Due to an overall scarcity of resources, healthcare budgets compete with other areas such as defence, housing and education, besides different healthcare services are in competition with each other. Therefore, decision-makers need scientific evidence to choose between two or more alternatives. Economic evaluations provide a systematic methodology to compare the costs and benefits accruing from different healthcare services or interventions (Drummond et al., 2015).

Economic evaluations in healthcare aim to assess whether it is worth allocating certain amount of resources on a particular service or intervention by considering all other alternatives that would not be funded if the option subject to investigation is preferred. This is called opportunity cost which is based on the assumption that the healthcare service budget is fixed and funding a novel service or intervention results in displacing another (NICE, 2013b).

Healthcare decision-making often relies on economic evaluations of public health interventions and health technologies. The use of economic evaluations for decisions on drugs varies across countries (Franken et al., 2012, Oortwijn et al., 2013). Australia was the first country to make economic evaluations a mandatory part of drug reimbursement decisions in 1992 (Pharmaceutical Benefits Advisory Committee Australia, 2016). Similar requirements have been issued by some other countries (ISPOR, 2002). Notably, relatively less regulations exist for economic evaluations of public health interventions (e.g. vaccines) and technological device assessments, compared to drugs (Edwards et al., 2013). Some countries have regulatory bodies which make decisions on health technology assessment based on economic evaluations (WHO, 2008). In England, the guidelines published by NICE identify the standard practice for economic evaluations (NICE, 2013a), and there are also NICE guidelines specific to the economic evaluations of public health interventions (NICE, 2013b).

3.1.2 Theoretical Foundations of Economic Evaluations in Healthcare

Economic evaluations in healthcare use the approaches of positive economics to inform resource allocation and the desirability of outcomes (Morris et al., 2012). However, their results are normative by nature because different methods are used dependant on the policy-makers' preferences, and value judgements are incorporated. Health economic methods are grounded in two approaches, namely welfarism and extra-welfarism. The key premises of those theories are presented in Table 3.1.

Table 3.1: Welfarism and extra-welfarism

Premise	Welfarism	Extra-welfarism
Rational-agent	Individuals are rational decision-makers aiming to maximise their welfare	Individuals are rational decision-makers aiming to maximise their welfare
Individualism	The best judge of individual welfare is the individual	The best judge of individual welfare is the individual
Aim of a healthcare system	Maximising total utility derived from health	Maximising total health
Outcomes	Individual utility	In addition to individual utility, health gains, distributional equity, impacts on carers could also be included
Source of outcomes	Affected individuals	All members of a society
Health outcome measure	Monetary values	Health gains (e.g. health-related quality of life)
Methods	Cost benefit analysis	Cost-effectiveness, cost-utility analysis

Source: The author's own summary based on the studies cited in the text

Welfarism is one form of consequentialism which suggests that decisions and actions should be judged based on their impacts on social welfare, and that social welfare is a function of individual welfare (Hicks, 1939). Welfarism sets out a framework to determine the desirability of a particular state of the world over another. The main pillar of welfarism is that the "goodness of any situation (e.g. a health state) should be

judged solely on the basis of the utilities attained by the group of individuals affected by the situation" (Hurley, 1988, p.377). A key premise of the welfarist approach is the Potential Pareto Improvement; that is resources should be allocated in a way to maximise the overall utilities; which could be achieved by (i) everyone being made better off or (ii) one individual being made better off without another being made worse off (Tsuchiya and Williams, 2001). The most obvious limitation of the Pareto Improvement is that it cannot address distributional equity.

The economic theories behind welfarism have been criticised strongly because some specific features of healthcare that distinguish it from other markets (Morris et al., 2012). Those are agency relationships (medical professionals act as an agent), moral hazard (individuals who have health coverage demand more healthcare services), supplier-induced demand (medical professionals know more than patients) and externalities (benefits to other individuals). Additional criticisms stem from the difficulty of valuing health in monetary terms (Ryan et al., 2003). Furthermore, it does not allow interpersonal comparisons or the incorporation of societal values (e.g. regarding health equity) (Coast et al., 2008, Hall et al., 2006, Kaldor, 1939).

Building on the critique of welfarism, extra-welfarism moves from the idea of maximising utilities derived from health to the maximisation of health itself. Brouwer (2008) summarises the key differences between extra-welfarist and welfarist approaches in terms of four aspects; (i) using outcomes other than utility, (ii) using preferences of individuals not affected by a certain status, (iii) weighting outcomes based on principles other than preferences and (iv) allowing interpersonal

comparisons of wellbeing. In extra-welfarism, quality-adjusted-life years (QALYs) are the main measure of health and the value of a QALY produced by a healthcare system is the same regardless of who receives it (Hurley, 1988).

Currently the economic evaluation methods that are most widely used adopt an extra-welfarist approach. In practice, the choice of theoretical approach translates as the choice of methodology. Descriptions of the most common methods used in health economic evaluation are provided below.

3.2 UNDERTAKING ECONOMIC EVALUATIONS IN HEALTHCARE

Comparison and capturing both costs and consequences are the prerequisites of undertaking full economic evaluations (Drummond et al., 2015). Comparison is the fundamental principle of economic evaluations, because one cannot decide whether to allocate resources on a new health service without having a criterion or an alternative. This alternative may be “no action” and it may be possible to compare providing a new intervention free at the point of service against doing nothing. The second principle is taking both costs and consequences into account.

An economic evaluation starts with identifying the decision problem and the important costs and benefits to take into account, depending on the chosen perspective (e.g. NHS, societal). The identified costs and benefits need to be valued. When assigning values to costs and benefits, the appropriate time horizon and discounting need to be considered. The next step is to estimate the incremental costs and benefits produced.

Lastly, the uncertainty around the findings needs to be considered. These concepts are explained below.

3.2.1 Costs and Benefits

Costs are usually investigated in two main categories (Rice, 1967, WHO, 2009b): direct and indirect costs. Direct costs are the most obvious costs accruing from any healthcare intervention, such as staff costs, investment costs and consumable materials. Indirect costs include productivity costs (e.g. lost workdays) and carer time which are harder to measure and the data are not always easily available. The types of costs used in health economic evaluations are presented in Table 3.2.

Table 3.2: Types of costs in health economic evaluations

Costs	Patient	Provider	Societal
Direct medical costs *(staff, consumables, etc.)*	YES	YES	YES
Direct non-medical costs *(transportation, etc.)*	YES	NO	YES
Indirect costs *(productivity costs, effects on the carer)*	YES	NO	YES
The author's summary based on Drummond et al. (2015)			

Health benefits could be measured as clinical impacts (or health impacts). These are measured in clinical terms, such as haemoglobin levels, carbon-monoxide levels, and number of quitters. The benefits of a health intervention or a treatment can also be measured in terms of its effects on people's overall wellbeing or quality of life. The QALY combines length of life with quality of life to develop utility values. The quantitative value of those utilities is used to compare the health benefits with costs.

3.2.2 Perspective

Perspective is a fundamental part of any health economic evaluation and it is identified based on the decision-maker to be informed by the evaluation (Drummond et al., 2015). Depending on the perspective chosen (e.g. *patient, provider and societal*), different costs are taken into consideration. For example, an economic evaluation from the patient perspective focuses on out-of-pocket payments by the healthcare user but from a healthcare perspective only the costs of providing a service would be of relevance. The perspective of an evaluation, therefore, affects the results obtained.

It is essential to clearly and correctly state the perspective of an economic evaluation regardless of the perspective choice. Being the most comprehensive, a societal perspective is generally considered the most valuable (Byford and Raftery, 1998, Jonsson, 2009). It captures costs and benefits beyond direct medical outcomes; that are important because health services often provide benefits to society which are broader than health (e.g. vaccination).

The type of healthcare system in a country has a huge influence on the costs to be included in an economic evaluation, for instance in the UK, direct medical costs may not constitute a significant amount from a patient's perspective because most health services are provided through a national healthcare system. Additionally, the perspective of an economic evaluation is often chosen based on the decision-maker for whom the evaluation is conducted. In some countries (e.g. Netherlands), the standard practice is to conduct an economic evaluation from a societal perspective. In

the UK, most economic evaluations use a provider perspective, namely the NHS perspective as recommended.

3.2.3 Valuing Costs and Benefits

The unit costs ideally are equal to the opportunity costs which are often reflected by market prices (HM Treasury, 2013). In the UK, the common practice is to utilise the NHS reference costs (NHS, 2019a) as unit costs, or those reported by the Personal Social Services Research Unit (Curtis and Burns, 2018). These are the average cost incurred in providing NHS services.

The valuation of health outcomes is often undertaken using health utilities which are estimated based on the preferences of individuals for different health states (Torrance, 1986). Health utilities are defined with zero being death and one representing a year in full health. Standardised questionnaires are used for estimating utilities, e.g. EQ-5D (Brooks, 1996), the Health Utilities Index (Torrance et al., 1995). These utilities are then used to calculate QALYs (Brazier et al., 2007). For example, if a person with the health utility of 0.80 is expected to live 20 years in that health state; the health outcome would be 16 QALYs. Although there are criticisms over the use of QALYs, they remain the standard tool for many government agencies including NICE. When comparing health benefits produced by two different interventions the incremental QALY gain is used.

3.2.4 Time Horizon

The time horizon of an evaluation refers to the duration covered when estimating costs and benefits, and the selected time horizon may have significant impacts on the findings (O'Mahony et al., 2015). For example, a drug, device or an intervention that is not cost-effective when only short-term costs and benefits are included, may be cost-effective once future costs and health benefits are considered.

The ideal time horizon is the whole duration over which an intervention is expected to have an impact (Cohen and Reynolds, 2008). For chronic diseases, longer time horizons (e.g. lifetime) are needed while for acute conditions (e.g. influenza) shorter time horizons may be appropriate. Furthermore, some healthcare interventions have intergenerational impacts, for example, smoking cessation during pregnancy would create health benefits not just for the mother but also for the infant and as a result, the appropriate time horizon would be the lifetime of the infant. NICE recommends using a lifetime approach albeit this often requires making assumptions (NICE, 2013b). For instance, the risk of experiencing a health condition may change over ten years but it may be assumed to stay stable over time.

3.2.5 Discounting

After deciding which future costs and benefits to include, it is critical to identify a price year and convert all the costs and benefits expected to accrue in the future into that year's values. This practice is called discounting and it has significant influence on the findings of an economic evaluation (Torgerson and Raftery, 1999). This is done based

on the assumption that people value future gains and losses less than those occur now, namely *time value of money theory* (Smith, 1953). This implies that gaining £100 today is more valuable than having it next year because one could use it during that time and as a result, one needs to subtract the value of waiting for one year from £100 to find the exact value of it next year. If the discounting rate is 10% yearly, £110 would be needed next year for the same value as £100 today.

Although there is consensus amongst health economists on discounting future costs, discounting future health benefits is a controversial issue. According to the time value of money theory, QALY gains obtained now are considered more valuable than the same QALY gains next year. By contrast, some researchers argue that health benefits should not be discounted because it is not possible to invest today's health gains in order to obtain future benefits, unlike saved costs (Gold, 1996, Ganiats, 1997, Sheldon, 1992). Discounting health benefits is a significant concern especially for health interventions which provide intergenerational health benefits (Jit and Mibei, 2015), e.g. smoking cessation. However, if future health benefits are not discounted, this implies that health gains achieved this year are equal to those obtained after 30 years. Due to the risk of overestimation, many health economists think future health benefits should be discounted as well as future costs (Drummond et al., 2015).

A further disagreement exists on the appropriate discounting rates. A systematic review of the relevant guidelines and studies reported that discounting rates ranged between 0% and 7% (Smith and Gravelle, 2001). This shows that some economic evaluations assumed that the value of present gains and losses were equal to future

gains and losses. WHO recommends using a 3% discount rate for both costs and health benefits (WHO, 2009b). In the UK, although the Department of Health has suggested using a lower discounting rate (1.5% to 2%) for health benefits (Department of Health, 2004), currently the standard discounting rate is 3.5% for both costs and benefits (NICE, 2013a). Additionally, NICE (2013b) recommends applying a 1.5% discount rate for public health interventions.

3.2.6 Cost-effectiveness Plane and Incremental Cost-effectiveness Ratio

The comparison of two alternatives in terms of their cost-effectiveness is often undertaken by placing them on a cost-effectiveness plane (Black, 1990), where the X axis represents effectiveness and the Y axis costs (Figure 3.1). If an intervention or treatment is less costly and more effective than the current standard (i.e. it falls into the south-east quadrant) it is said that the new treatment dominates the previous one. Conversely, if the new option is more costly and less effective (i.e. it falls into north-west quadrant) it is dominated by the current treatment.

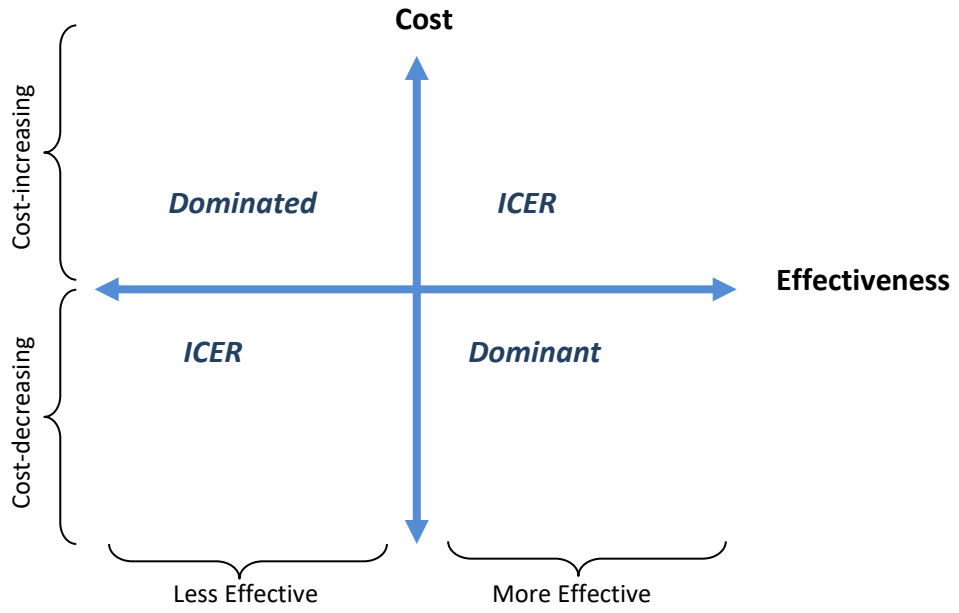


Figure 3.1: Cost-effectiveness plane (Adapted from Black et al. 1990)

If the new alternative falls into the north-east quadrant or the south-west quadrant, incremental costs are divided by health benefits to produce the incremental cost-effectiveness ratio (ICER). This can be formulated as follows:

$$ICER = \frac{Cost\ (new) - Cost\ (current)}{Benefit\ (new) - \ Benefit\ (current)}$$

The benefit in the calculation of ICER can be in different forms (Neumann et al., 2016); these include Life Years (LYs) as in cost-effectiveness studies or Quality Adjusted Life Years (QALYs) as in cost-utility studies. Additionally, in low-income countries mostly Disability Adjusted Life Years (DALYs) are used.

3.2.7 Cost-effectiveness Threshold

In the UK and in some other healthcare systems, incremental costs and QALYs are compared to a pre-defined cost-effectiveness threshold per QALY gained to decide whether a healthcare product or service is cost-effective (Towse et al., 2002). Different countries apply different cost-effectiveness thresholds and it is between £20,000 and £30,000 in the UK (Devlin and Parkin, 2004, Dubois, 2016, Neumann et al., 2014). The suggested figure by WHO for countries without a country-specific figure is the three times their GDP per capita per DALY averted (WHO, 2003). However, there is an ongoing debate about the limitations of these thresholds (Bertram et al., 2016).

The current value of the cost-effectiveness threshold in the UK (£20,000 to £30,000) is subject to a number of criticisms as summarised by Claxton et al. (2015). Firstly and most importantly, there is a view that the current threshold is not evidence based. Secondly, some authors argue that NICE should not set a threshold for cost-effectiveness under the assumption of a flexible budget but should search the optimal threshold within a set budget provided by the government. Additionally, the NICE threshold has not changed, despite considerable changes in inflation rates, NHS budgets and guidelines for economic evaluation studies. Lastly, there are some concerns over the value of the current threshold being too high, suggesting a lower threshold at £12,936 per QALY (Claxton et al. (2015). Nevertheless, currently it is standard practice to use the NICE threshold in UK-based economic evaluations.

3.3 ECONOMIC EVALUATION METHODS IN HEALTHCARE

Economic evaluation methods in healthcare can be categorised according to the study type and design (Cohen and Reynolds, 2008, Drummond et al., 2015), as summarised in Table 3.3.

Table 3.3: Methods of economic evaluations in healthcare

Classification	Economic Evaluations	Key Feature
Study type	Cost-benefit	Uses monetary measurements for costs and health outcomes
	Cost-effectiveness	Measures health benefits in natural units
	Cost-utility	Measures health benefits in various ways including quality-adjusted life years (QALYs)
Study design	Trial-based	Data is taken from clinical trials
	Model-based	Best available evidence is used
	Hybrid	Data acquired from trials is extrapolated with modelling
The author's own summary based on Cohen and Reynolds (2008) and Drummond et al. (2015)		

Based on the theoretical approach and the type of data used, economic evaluations generally take three forms: cost-benefit, cost-effectiveness and cost-utility studies (Drummond et al., 2015). Cost-benefit analysis measures both costs and health consequences in monetary terms. This analysis is useful when healthcare services are evaluated against other types of services (e.g. environmental services). However, assigning a monetary value to health outcomes possesses a significant difficulty and as a result, this type of evaluation has had limited use in health research.

Cost-effectiveness analysis evaluates different programmes or treatments in terms of benefits and costs. However, cost-effectiveness studies use natural measurements of health consequences such as life years gained and major complications avoided. Cost-

effectiveness analysis focuses on producing more of the desired outcome at the same cost, namely technical efficiency. Yet it is not possible to compare more than one health outcome, thus, as a result allocative efficiency, cannot be addressed by this type of evaluation. For example, cost-effectiveness analyses of smoking cessation interventions include outcomes such as the incremental cost per quitter, which is not comparable to other healthcare interventions (Jones et al. 2016). This is a critical drawback of cost-effectiveness analysis because decision-makers often need to make budget allocation decisions in healthcare.

Cost-utility analysis overcomes the disadvantages of cost-benefit and cost-effectiveness analyses. This method allows incorporating more than one health outcome and uses one generic measure instead of monetary values or natural health units. Health outcomes are mostly assessed with QALYs. Using a single measure allows comparison of different healthcare programmes, in turn addressing allocative efficiency. Cost-utility analysis, therefore, is recommended by organisations providing guidance to healthcare decision-makers, such as NICE in England Thus, it has been the most widely used method amongst economic evaluations published in peer-reviewed journals (Pitt et al., 2016).

On the other hand, the method has an important constraint that is the assumption of QALY is a QALY regardless of the recipient, ignoring concerns about health equity. Some recent techniques have been purposed to deal with this; for example it is possible to assign higher QALY values to specific groups of individuals (Cookson et al., 2017). Nevertheless, this requires important social value judgments including the

identification of inequality aversion levels in a society. The use of these methods has therefore, been very limited.

The choice of methods is important due to the implications on analysis findings; for example a cost-benefit analysis and a cost-utility analysis might result with contradictory recommendations for policy-makers (Buchanan and Wordsworth, 2015). In the UK, NICE recommends using cost-utility analysis, taking an extra-welfarist stance (NICE, 2013b).

Regarding data sources, some economic evaluations are conducted alongside clinical trials and this allows health economists to collect necessary data more efficiently (Petrou and Gray, 2011, Ramsey et al., 2015). Yet trial-based studies often have a limited time horizon and do not capture long-term cost and health impacts that may be important to decision-makers. Model-based evaluations can overcome this limitation of trial-based studies by extrapolating the costs and benefits over the long-term, until death (Briggs et al., 2006). To do so, however, economists may have to rely on secondary data and make many assumptions if the necessary information is not available. Many economic evaluations combine these two approaches (i.e. hybrid evaluations); they acquire data from clinical trials and make predictions using modelling approaches to estimate the overall impact of a treatment or intervention (Mason et al., 2002). These studies overcome the limited time horizon issue of trial-based evaluations and increase the accuracy and completeness of the data.

3.3.1 Model-based Economic Evaluations

Mathematical models are frequently used to estimate the costs and benefits of an intervention beyond the available data. Cohort-based models are used when there is no interaction between individuals; and this is the most common approach in decision analytic modelling (Buxton et al., 1997). There are also other modelling approaches. For example, discrete event simulations allow following individuals separately and modelling interactions between individuals (e.g. infectious diseases). Additionally, dynamic models are used to incorporate interactions between individuals without modelling each cohort member separately (Brennan et al., 2006).

Cohort models are conducted in two common forms: decision trees and Markov models. It is important to select the appropriate modelling approach depending on the research question (Barton et al., 2004). Decision trees are used if the timescale is short and the evaluated options (drugs, devices or interventions) have no impact on the mortality risks. Markov models, on the other hand, are preferred if there are long-term impacts (Beck and Pauker, 1983).

3.3.1.1 Decision trees

Decision trees are widely used in economic evaluations of healthcare interventions. A decision tree starts with a group of people. Potential decisions, probabilities and outcomes are represented in distinct branches. Figure 3.2 below demonstrates an example decision tree.

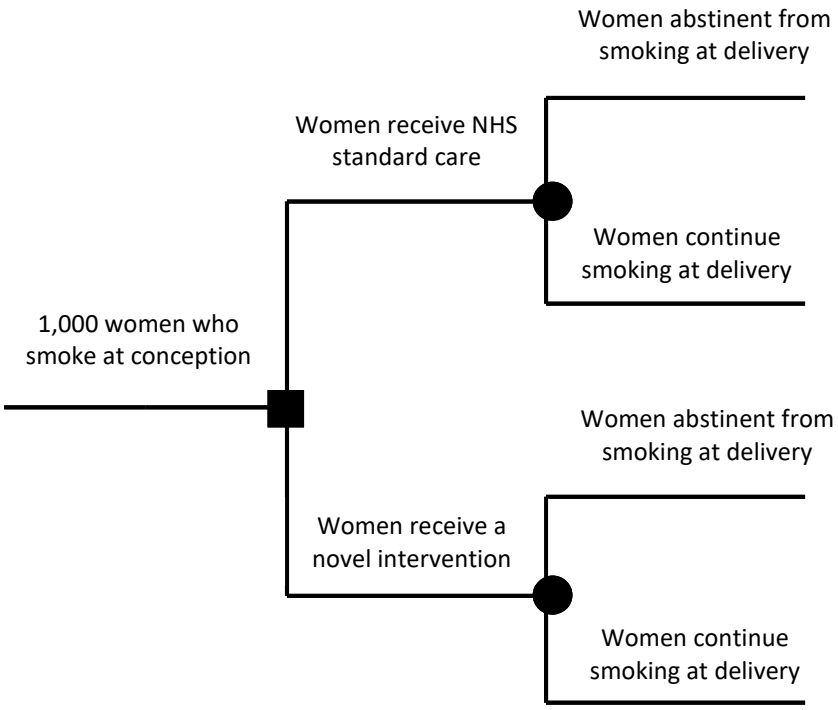


Figure 3.2: An example decision tree for a hypothetical intervention

The example decision tree starts with 1,000 pregnant women who smoke. There are two possible decisions for the women: receiving the standard NHS care or a hypothetical novel intervention. This is called the decision node (square) where a decision-maker can make a choice. After the decision, there are two potential outcomes in this example: women successfully quit smoking by the time of delivery or continue to smoke. This second node (circle) is the chance node where more than one outcome might occur. The probabilities of outcomes on the same node always sum to one.

The value of a specific decision is calculated by rolling back from right to left. In the example tree, there are four potential pathways for expectant mothers who smoke. To estimate the value of the two potential decisions benefits and costs are estimated for each pathway. For example, to estimate the number of women who become abstinent at the time of delivery, the probability of quitting at delivery is multiplied by the number of women in that branch. Similarly, the costs of both alternatives (NHS standard care and the novel intervention) are multiplied by the number of women to estimate the cost of each decision.

Decision trees are useful tools if the intervention does not have long-term effects and there is limited number of pathways. The simple structure of decision trees allows easy interpretation. However, this method possesses difficulties when the outcomes are longitudinal, as hundreds of branches may be required (Sonnenberg and Beck, 1993).

3.3.1.2 Markov models

In this type of analysis, individuals are grouped into several health states (e.g. healthy, ill, dead). The probability of an individual being in each of those states and the probability of transitioning from one state to another in a certain time period (e.g. one year) are estimated based on trial data or the published literature. Figure 3.3 below demonstrates a simple Markov model.

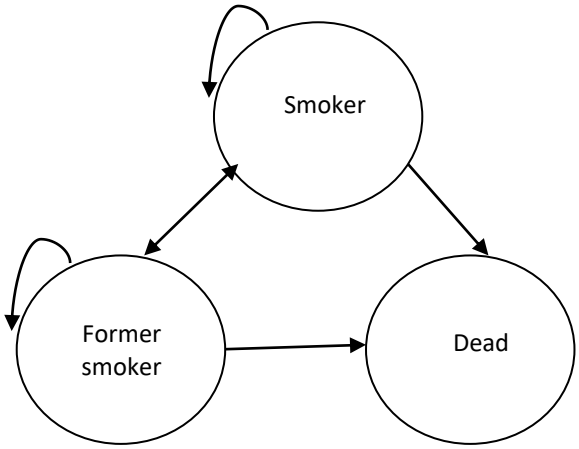


Figure 3.3: An example Markov model

The probabilities of being in different states sum to one. Individuals can transit between smoker and former smoker states or stay in the same state until death. In each cycle, the number of individuals in each state is calculated. The benefits and costs associated with a specific intervention is the sum of the benefits and outcomes in all states in each cycle.

Markov models have flexible structures that enable estimating the long-term impacts of healthcare interventions. Yet, the most important limitation of Markov models is their memoryless nature, namely Markovian assumption, which implies that the previous state of a patient or the duration spent in a state has no impact on transition probabilities. For example, in the example model in Figure 3.3, it is not possible to incorporate the impact of the duration of staying abstinent from smoking on the probability of restarting to smoke.

3.3.2 Using Economic Model-based Evaluations to Inform Decision-making

Economic models contribute to healthcare decision-making in several ways (Drummond et al., 2015). Firstly, models allow comparing all relevant options, which is often not possible with trial-based evaluations. Economic evaluations which do not consider all alternatives may mislead decision-making. In model-based evaluations, it is possible to consider all relevant alternatives by modelling hypothetical scenarios.

Another consideration is that the existing evidence from trials may not always relate to a specific decision. Model-based evaluations can bridge that gap by combining data from different sources under explicit assumptions (Drummond et al., 2015). For example, a cost-effectiveness study based on a specific SDP intervention may not consider the impact of second-hand smoking (SHS) by a partner during pregnancy. It may be possible to incorporate that into an economic model.

Moreover, as stated in Section 3.3, it is possible to extrapolate the trial results over long-term, using economic models (Briggs et al., 2006). Decision-making based on economic evaluations with a short time horizon might lead to suboptimal or wrong decisions. This is especially important for many public health interventions such as smoking cessation interventions for pregnant women. An economic evaluation relying on a trial which ends at the time of delivery would not be able to consider the long-term benefits of SDP interventions, such as the reduced risk of asthma amongst infants. If long term impacts are not taken into account, this can contribute to sub-optimal resource allocation decisions.

3.4 DEALING WITH UNCERTAINTY

There is often considerable uncertainty around the findings of economic evaluations, which may arise from parameter uncertainty and the structure of the evaluation (Drummond et al., 2015). Parameter uncertainty defines the lack of the true values of the evaluation inputs, which may be caused by variability, sampling errors or measurement errors while structural uncertainty refers to the uncertainty caused by the chosen methods for the evaluation. Estimating uncertainty is important to demonstrate the level of confidence in the decisions to be made based on an economic evaluation. To estimate the level of uncertainty, a sensitivity analysis is conducted. This allows the identification of the variables which cause the greatest uncertainty. Additionally, it enables researchers to reflect on the controversial issues in the literature (e.g. discounting rates).

Health economists undertake sensitivity analyses in different ways (Briggs et al., 1994). One method to conduct a sensitivity analysis is to vary one input each time (one-way sensitivity analysis) while the others remain unchanged. This method is simple to apply and more flexible than the other techniques, but it often provides an underestimation of the level of parameter uncertainty (Secker-Walker et al., 2002). The second method is to vary more than one parameter at a time (multi-way sensitivity analysis), which becomes complicated if the variables are not independent from each other. Another technique is conducting a scenario analysis, a type of multi-way sensitivity analysis where the base-case and cautious-case scenarios are compared. However, identifying plausible alternative values can be challenging. The most widely recommended

method of dealing with uncertainty is to conduct a probabilistic sensitivity analysis (PSA). A PSA involves a significant amount of Monte Carlo simulations where several parameters are varied randomly alongside predefined distributions around parameter values (Gold, 1996). The choice of distributions is informed by the nature of the parameters; for example, the Gamma distribution is used for cost parameters because it is a continuous and right skewed distribution (Drummond et al. 2015).

Following debates on the adequacy of the standard methods of sensitivity analyses a different method was developed (Briggs et al., 1997, Briggs and Gray, 1999, Van Hout et al., 1994). This method estimates the probability of cost-effectiveness at different WTPs based on the joint distribution of costs and benefits produced by the PSA (Fenwick et al., 2004). This produces a graph called a cost-effectiveness acceptability curve (CEAC). CEACs are widely used in cost-effectiveness and cost-utility analyses (Fenwick et al., 2004, Meckley et al., 2010). However, the use of CEACs is criticised because they do not present the differences in the net benefits (i.e. benefits after the subtraction of costs) of the alternatives, and additional tools (e.g. incremental net benefit estimations) are suggested to overcome these limitations (Drummond et al., 2015).

3.5 EXPECTED VALUE OF PERFECT INFORMATION ANALYSIS

Economic evaluations are produced based on the best available evidence which is not perfect due to limitations and uncertainties. This may lead to suboptimal decisions in

healthcare. It is possible, however, to estimate the value of reducing uncertainties by gaining additional information using the results of PSA (Claxton and Posnett, 1996).

Expected value of perfect information (EVPI) is described as the net benefit of making a decision under no uncertainty (Wilson, 2015). Estimating EVPI can be illustrated with an example (Tuffaha et al., 2014), if an economic model estimates that the net benefit of intervention A (£1,200) is greater than the net benefit of intervention B (£1,000), the decision would be to choose option A. However, the probabilistic sensitivity analysis shows that the intervention would not be cost-effective in two scenarios out of five, which means there is a 40% probability that choosing option A is a wrong decision. The average difference between the net benefits of the two options in every scenario when A is chosen would be the EVPI.

If the cost of additional research is greater than the EVPI, the evidence produced by the economic evaluation would be considered sufficient to make an optimal decision. If the cost of additional research is lower than the EVPI, the research may be funded by decision-makers. Therefore, EVPI analysis provides an analytical framework for deciding whether further research is needed.

3.6 LIMITATIONS OF ECONOMIC EVALUATIONS IN HEALTHCARE

Economic evaluations are not without limitations. Firstly, they often rely on secondary data and in some situations where the data is not available economists may need to make some assumptions, which can affect the accuracy of the evaluations. A review of the economic evaluations of drugs in Western Europe found that in 17 out of 27

evaluations, ICERs varied to the extent of changing the decision on funding the drug (Barbieri et al., 2005). Correspondingly, some authors have made calls to standardise reporting economic evaluation studies (Husereau et al., 2013).

The use of economic evaluations within decision-making is limited as well. This is caused by factors relating to decision-makers, context and economic evaluations (Lessard et al., 2010). In some countries, conducting an economic evaluation is not an obligatory part of healthcare decision-making (Tunis, 2004, Torbica et al., 2018). The use of economic evaluations, therefore, might be limited in these settings. However, even in the countries where economic evaluation is mandatory for reimbursement decisions, such as in Australia and UK, the use of economic evidence is somewhat restricted, especially at a local level (Drummond, 2004, Eddama and Coast, 2008). A qualitative study investigating the usefulness of economic evaluations for decision-makers raised concerns over the quality of evaluations and the generalisability of their findings (Hoffmann et al., 2002). Nevertheless, economic evaluations have been increasingly considered for decision-making across the world (ISPOR, 2002). Drummond (2004) suggests four significant elements to increase the use of economic evaluations; a clearly defined decision-making process, clear policy objectives, applicable timelines, adequate resources, and sufficient incentives.

Further concerns arise around the transferability of economic evaluations conducted in one jurisdiction to another. For example, according to the guidelines of 27 countries, baseline risks and unit costs have low transferability across jurisdictions as opposed to treatment effect which is considered to have high transferability (Barbieri et al., 2010).

Similar results are reported in a study investigating the transferability of economic evaluations undertaken in high-income countries to middle-income countries and the biggest challenge was the differences in patterns of care. Governments and researchers have produced some guidelines to overcome those limitations (Drummond et al., 2009, Welte et al., 2004).

Pitt et al. (2016) reported that more than 1,200 economic evaluations are published annually. Hence, economic evaluation in healthcare is still a developing area and the field is expected to grow owing to healthcare decision-makers' requirement for scientific evidence at central and local levels. Regarding the methodology of economic evaluations, there is emphasis on the need for transparency and a contextualised approach in order to provide useful data for decision-makers (Husereau et al., 2013).

3.7 RETURN ON INVESTMENT

Due to the limitations of traditional approaches to economic evaluations, some additional tools are used when evaluating health interventions. Return on investment (ROI) is an economic measure to assess the efficiency of an intervention. ROI is calculated as the net benefit that is the benefits (however defined) divided by the cost of an intervention (NICE, 2011a). It is possible to estimate the economic returns at various payback timescales (e.g. one year, lifetime). For instance, it was estimated that every £1 invested in smoking cessation services in Lancashire would generate £2.82 over 10 years and £9.35 over a lifetime (LGA, 2013).

Currently, there is no guidance or consensus on good conduct regarding ROI analysis. NICE has generated some ROI tools, such as the Tobacco ROI tool to inform local decision-making (Pokhrel et al., 2014). This tool estimates different types of ROI. For example, one measures benefits in terms of healthcare cost savings and productivity savings while the other includes health gains by assigning a monetary value (£20,000 per QALY gained).

ROI is increasingly used to demonstrate the value of health programmes and local decision-makers are interested in ROI to advocate for funding of health interventions due to budget constraints (Brousselle et al., 2016, Masters et al., 2017). Hence, estimating ROI alongside cost-effectiveness would increase the evidence produced by economic evaluations.

3.8 ECONOMIC EVALUATION OF SDP INTERVENTIONS

A systematic review of economic evaluations for smoking cessation programmes aimed at pregnant women identified important gaps in the literature (Jones et al., 2015). All assessed interventions were provided for a short period of time and they were mostly low intensity interventions. Therefore, there was a lack of evidence on the cost-effectiveness of providing a long-term and more intensive support for pregnant women.

The key outcome of interest was abstinence at delivery. Outcomes were often measured at around four-week post-randomisation and at delivery. Some economic evaluations also reported postpartum abstinence (Boyd et al., 2016, Cooper et al.,

2014b, Dornelas et al., 2006, Ussher et al., 2015). However, the abstinence rates were based on self-reported data and not biological verification.

Smoking was mostly identified as a binary condition. Only four studies categorised smokers according to the number of cigarettes consumed (Dornelas et al., 2006, Pollack, 2001, Ershoff et al., 1983, Taylor, 2009). One study found 75% of women who were smoking less than 20 cigarettes daily quit by delivery, whereas this figure was 30% for those smoking 20 or more cigarettes (Ershoff et al., 1983).

Regarding healthcare costs, infant costs were included in most evaluations (Ruger et al., 2008, Thorsen and Khalil, 2004, Windsor et al., 1993, Ershoff et al., 1983, Ershoff et al., 1990, Shipp et al., 1992, Taylor, 2009, Mallender et al., 2013) although studies often focussed on the short-term costs arising from conditions such as low birth weight (LBW) or sudden infant death (SID).

Some studies included the costs arising from the medical care provided for the mother (Cooper et al. 2014b; Mallender, 2013; Shipp et al. 1992; Thorsen and Khalil, 2004; Taylor, 2009). Among those, only two included long-term health conditions while most of them covered pregnancy-related conditions. Mallender et al. (2013) also calculated productivity costs based on the information that a smoker is likely to be absent from work for 22 additional hours annually compared to a non-smoker.

3.8.1 Decision Models of SDP Interventions

The review by Jones et al. (2015) included most of the decision analytic models published to date (Hueston et al., 1994, Marks et al., 1990, Mallender et al., 2013, Shipp et al., 1992, Taylor, 2009). The review indicated some serious limitations with existing models such as a short time horizon, limited consideration of uncertainty, high relapse rates and omissions of some significant health conditions. Two UK-based models were built after the publication of this review (Boyd et al., 2016, Jones, 2015). Additionally, the NICE ROI tool developed for smoking in the general population, also included pregnant smokers (Pokhrel et al., 2014). However, that tool only captured the healthcare costs accrued during the first five years of the children. Moreover, none of the models considered the potential benefits of the SDP interventions on individuals who live with smoking women, such as the reduced SHS exposure. Table 3.4 below summarises the main features of these models.

Table 3.4: Main features of the previous models

Author & Year	TIME HORIZON	INCLUDED HEALTH RISKS AND COSTS	INTERVENTIONS	IMPACT OF SHS	MODEL STRUCTURE	MAIN FINDINGS
Boyd 2016	Lifetime-mother	Cost per related death, intervention costs (Post-birth hospitalisation costs for premature and low birth weight babies were included, and long-term cost of treating smoking related diseases was incorporated in a scenario analysis)	NRT + Financial incentives	NO	Cohort simulation model	ICER was £1,127 per quitter and £482 per QALY.
Hueston 1994	Outcomes at birth	Intervention costs and medical care costs for LBW	Behavioural	NO	Decision tree	$80 in 1989 prices was found to be the cost-effectiveness threshold for smoking cessation interventions with 18% quit rate.
Jones 2018	Lifetime-mother and infant	Pregnancy related problems except for PPROM, LBW, preterm birth, foetal loss Women lifetime model included CHD, COPD,LC, stroke Childhood model included only asthma	Can be applied to any intervention SNAP trial was tested in the thesis	NO	*Three components:* -Pregnancy mother and infant (decision tree) -Mother and infant lifetime (Markov chains)	ICER per quitter was estimated as £2,932.10 (was £4,156 within trial estimate).
Mallender 2013	Lifetime-mother	Mother (ectopic pregnancy, spontaneous abortion, pre-eclampsia, placenta previa, abruption placenta and PPROM, CHD, COPD, Lung Cancer, MI, Stroke), productivity costs and infant medical costs (LBW, SID, Asthma, Otitis)	Behavioural, pharmacological financial	NO	*Two models:* -Short-term; decision tree -Long-term; cohort simulation including males and females	All types of interventions were found to be cost-effective at £30,000 per additional QALY.

Table 3.4: Main features of the previous models (continued)

Marks 1990	Lifetime-mother	Perinatal death, LBW, Lifetime health burden of LBW	Hypothetical intervention based on previous trials	NO	Cohort simulation model	Benefits/cost ratio =1/3.26
Pokhrel 2009 (NICE ROI tool)	Lifetime-mother & five years of the children	Costs in the first five year of the children	Any	NO	Cohort simulation model	Can produce ICERs and ROI
Shipp 1992	Outcomes at birth	Pregnancy related costs at delivery, LBW and preterm delivery and intervention costs	Behavioural	NO	Two decision trees, one for the mothers one for infants	$32 in 1989 prices was cost-neutral.
Taylor 2007	Lifetime-mother	Hospital admission costs for the first five years of life (children) Lung cancer; CHD; COPD; MI; Stroke (mother), Intervention costs	Behavioural, pharmacological stages of change	NO	Cohort simulation model	*Cost per QALY:* £4,005- CBT £2,253-pharmacotherapy £1,992-feedback £2,253-stages of change Rewards and other interventions were dominant over the standard care.

The Economic impacts of Smoking In Pregnancy (ESIP) model developed by Jones et al. (2018) overcame some of the limitations of the previous models. It was the first dynamic model allowing interaction between the mother's smoking behaviour and the infant's health. It included the lifetime impacts on mother and infant for the first time and considered the increased probability of smoking uptake among the children of smoking mothers. However, the ESIP model still had some limitations, such as omission of some health conditions and a binary identification of smoking.

3.8.1.1 How could the ESIP model be improved?

The evidence around the key limitations of the ESIP model (Jones 2015; Jones et al. 2018) was examined to understand whether building a new economic model merited value to obtain more accurate health economic evidence.

1. Health conditions: Health conditions incorporated in the ESIP model were defined based on a scoping review covering studies published up to July 2011 (Jones 2015). The studies were assessed based on evidence of a causal link, but although a causal link was identified for birth defects and sudden infant death (SID) they were not included in the model due to their low prevalence in the society. Similarly, respiratory diseases other than asthma were not considered. Thus, the ESIP model could potentially underestimate the benefits of SDP interventions. Furthermore, it was possible to identify new evidence regarding the conditions included in the ESIP model, considering that a significant amount of time had passed. Therefore, it was judged that an updated review of the literature was needed to identify the health conditions to be included in the new economic model.

2. The impact of former smoking: The ESIP model assumed that women who quit just before pregnancy had the same risks as those who never smoked. However, there is evidence showing that being a former smoker increased the risk of ectopic pregnancy and the mortality and morbidity risks outside pregnancy (Bouyer et al. 2003, Doll et al. 2004, Malek et al. 2015). Therefore, by omitting the impact of former smoking behaviour, the ESIP model potentially underestimated the benefits of SDP interventions. The new model sought to address this issue.

3. Exposure window: One potential improvement was to extend the model and capture the smoking behaviour before delivery to include the impact of timing of cessation. Systematic reviews found no difference between pregnant women who quit early in pregnancy and non-smoking women in terms of health outcomes (Agutu, 2012, Nicoletti et al., 2014), showing that women who quit early in pregnancy had the same risk as those who did not smoke. Hence, the assumption in the ESIP model was justified.

4. Second-hand smoking: The ESIP model did not include the impact of SHS by partners on women, despite its impact on women's behaviour change (Prady et al., 2012) and health outcomes (Salmasi et al., 2010). There is sufficient evidence showing the impact of SHS on health outcomes during and after pregnancy (Liebrechts-Akkerman et al., 2011, Pineles et al., 2014, Pineles et al., 2016), and therefore it was decided that the ESIP model could be improved through adoption of a household perspective (women, their partner and offspring). Similarly, the impact of SDP interventions on partners was not considered in ESIP. Hence, it was decided to include

the impact of SHS on partners by women and the probability of quitting smoking amongst smoking partners.

5. Reducing smoking: The ESIP model included only two outcomes for a cessation intervention, quitting or resuming smoking. However, evidence from several trials shows a positive relationship between the number of cigarettes consumed and increased health risks (Aliyu et al., 2011, Pineles et al., 2014, Pineles et al., 2016). Thus, a reduction in smoking is an important achievement that needs to be considered in economic evaluations of SDP interventions.

It is also known that people who reduce smoking are more likely to quit in their succeeding attempts (Begh, Lindson-Hawley and Aveyard, 2015). A reduction in the number of cigarettes therefore is an important consideration and this factor has been previously incorporated in an economic model designed for the general population, and characterised as "cut down to quit" (Wang *et al.*, 2008). Hence, it was evident that including the impact of reducing smoking in the new model could be a substantial improvement to the ESIP model.

6. Number of quit attempts: Women were allowed to make only one quit attempt in some models (Boyd et al. 2016, Taylor, 2009). Conversely, in the ESIP model women were able to make a limitless number of quit attempts. However, the evidence from the Surgeon General's Report suggested that women succeeded to remain abstinent on average after 6.3 attempts (CDC, 2001). Jones (2015) demonstrated the computational difficulty of incorporating this into an economic model, partly caused by

the Markovian assumption. Thus, it was not possible to reflect this reality in the new model.

7. Relapsing: Regarding relapse rates, the model developed by Taylor et al. (2008) assumed 70% of all women who had quit smoking would relapse to smoking in a year, and no further relapses would occur. On the other hand, another model assumed a zero relapse rate (Mallender et al., 2013). Boyd et al. (2016) incorporated a relapse rate for non-pregnant women up to eight years following pregnancy. Considering these limitations, Jones (2018) used postpartum-specific abstinence rates (53%, one year after delivery). However, the biologically verified relapse rate was reported to be higher (80%) than the figure used in the ESIP model (Ratner et al., 1999). Furthermore, the ESIP model did not allow the user to enter different postpartum abstinence rates although these figures are very likely to be different for different interventions due to variations in intervention design and duration. Hence, adding this feature to the model was also considered to be a necessary improvement.

In response to the evidence around the key limitations, it was appropriate to build a new model by restructuring the ESIP model. The new model would include additional health outcomes, the impact of former smoking, partners' smoking, the heaviness of smoking (henceforth referred to as "severity of smoking"), and better data on postpartum relapse rates.

3.9 CONCLUSION

There is evidence showing the cost-effectiveness of SDP interventions in the short-term. The long-term outcomes, however, are not well-known. The SDP interventions published to date were low-intensity, short-term and low-cost interventions. As discussed in the previous chapter, the impact and reach of those interventions was very limited. Thus, evidence on the cost-effectiveness of high-intensity, long-term and more costly interventions is needed.

The most comprehensive economic model of SDP interventions is the ESIP model, however some limitations remain. Therefore, it was appropriate to work on its limitations and produce a more comprehensive model to conduct a more accurate economic evaluation of SDP interventions. The first step for this was to identify the health outcomes of SDP on mothers and infants.

CHAPTER 4: HEALTH OUTCOMES OF SMOKING DURING PREGNANCY AND POSTPARTUM PERIOD: AN UMBRELLA REVIEW

4.1 INTRODUCTION

As discussed in Section 3.8, the economic evaluations of SDP interventions conducted to date have included a limited number of health conditions only, and there has been no consistency in terms of the health outcomes included. Additionally, there was no systematic overview of all health impacts of smoking on mothers and infants to inform economic evaluations of smoking cessation interventions aimed at pregnant women. Therefore, a systematic review (umbrella review) was conducted to identify the relevant evidence to inform the economic evaluation of SDP interventions.

In this chapter, firstly, systematic reviews and umbrella reviews are described. Then, the need for an umbrella review on the health outcomes of SDP and the postpartum period is discussed. The following sections present the methodology and findings of the review. Next, the identification of the health conditions to be included in the economic evaluation is explained.

4.1.1 Systematic Reviews and Umbrella Reviews

Systematic reviews present all available scientific evidence according to a set of pre-defined criteria in order to answer defined questions. They are increasingly used to inform decision-makers, and 11 systematic reviews were published every day in 2010 (Bastian et al., 2010). Systematic reviews differ from the traditional literature review in the way that they have a clear road map prior to the research, and every step of the review is reported transparently, therefore reducing bias and providing reliable and valid evidence (Higgins and Green, 2011).

Systematic reviews are considered a higher level of evidence than trials because they provide an overview the whole picture and eliminate bias. However, there are some concerns about the rigour and quality of systematic reviews (Moher et al., 2015). As a way to overcome the issues of biased or unpublished systematic reviews, review protocols are recommended. Protocols set out the objectives and methods of the reviews, and they are used as a guideline during the review process. Therefore, a sound systematic review should have a publicly available protocol designed and published prior to the research.

Although systematic reviews provide a robust summary of the available evidence, it is not rare that different systematic reviews on the same topic report inconsistent findings. This may be the case once the number of systematic reviews around an issue has increased significantly. Under these circumstances, health decision-makers would need an overview of reviews. Umbrella reviews, sometimes called “systematic review of reviews” or “overview of reviews”, can be defined as utilising evidence from several

reviews of observational studies to present a robust picture of the state of art (Higgins and Green, 2011; JBI, 2014). Umbrella reviews follow similar methods to systematic reviews of observational studies but only include reviews. Umbrella reviews provide the opportunity to summarise the evidence from different analyses of the current evidence for several health outcomes (Higgins and Green, 2011). Therefore, they are particularly useful to answer broader questions than the systematic reviews. Moreover, umbrella reviews can identify the gaps for future systematic reviews.

4.1.2 The Need for an Umbrella Review

A systematic approach was required to identify robust evidence to inform the economic evaluation of SDP interventions. There were numerous systematic reviews investigating the impact of SDP on a particular health condition. However, the studies often reported contradictory findings. Thus, an overall examination of the current evidence was required.

Several narrative reviews have surveyed the short and long-term effects of maternal SDP and the postpartum period. Among them, the most recent and comprehensive one by Jones (2015) included studies published until July 2011. The focus of that review was not systematic reviews and a quality assessment of the included studies was not conducted. Moreover, a considerable amount of time passed since its publication, and it was very likely that more updated evidence on the topic was available. Therefore, it was necessary to undertake an umbrella review to identify the evidence on the effects of SDP and the postpartum period on mothers and infants.

4.1.3 Objectives of the Umbrella Review

The primary objective of this umbrella review was to identify the health impact of SDP and the postpartum period on mothers and infants to inform the economic model. Additionally, the review evaluates the evidence for model parameters regarding the impact of number of cigarettes consumed during pregnancy and second-hand smoking (SHS) by the mother's partner during pregnancy.

4.2 METHODS

The protocol explaining the methodology of this review was submitted to PROSPERO (CRD42018086350) and published (Saygın Avşar et al., 2018). The review was designed in line with guidelines provided by Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011).

4.2.1 Inclusion and Exclusion Criteria

This review focussed on the health outcomes of SDP, including all studies involving pregnant or postpartum women who smoke in high-income (HICs) and middle-income countries (MICs) with no age restrictions. The comparator was defined as pregnant or postpartum women who have never smoked or who have quit smoking.

Only full-text, systematic reviews published in a peer-reviewed journal were included in the review. The primary outcome measures for this review were the health outcomes associated with smoking during pregnancy and the postpartum period for

the mother and infant. Outcomes could be odds ratios (OR) and relative risks (RR) for smoking women and their children compared to non-smoking women and their children. This included pregnancy-related clinical problems and long-term adverse health outcomes for the infant.

Although there was a wide literature around the topic, only studies that adhered to the objectives of this review were selected for the analysis. Exclusion criteria were identified as follows:

- Studies focussing on low-income countries (LICs) were excluded due to significant differences in healthcare systems.
- Studies which focus on the psychology of SDP or barriers to cessation and genetic studies were excluded.
- For pragmatic reasons, studies which were not published in English were excluded.

4.2.2 Search Strategy

Firstly a scoping search was conducted using following steps:

1- A limited search of MEDLINE with the words of "pregnant women, pregnant smokers, maternal smoking, health outcomes, cost outcomes, QALYs" and InterTASC Information Specialists Sub-Groups (ISSG) filter to identify keywords were applied by using a PICO approach. Additionally, the keywords of 5 systematic reviews in relevant topics were searched.

2- Identified keywords were discussed with two experts to crosscheck. Those search terms are provided in Table 4.1.

Table 4.1: Boolean search terms

Concept A	Concept B	Concept C	Concept D
Pregnan*	Smok*	Pregnancy outcomes	Systematic Review
Postpartum	Tobacco	Birth outcomes	Meta-analysis
		Infant outcomes	
		Childhood outcomes	
		Adverse outcomes	
		Long-term outcomes	
		Quality of life	
		Quality adjusted life year	
		Health Outcomes	

The literature search strategy was undertaken as follows:

1- Selected keywords were utilised in the extensive literature search. The configuration of Boolean operators (AND, OR) is illustrated in Figure 4.1.

2- The inclusion and exclusion criteria were piloted by the reviewers independently in order to maximise the consistency of the study selection process.

3- CINAHL, EMBASE, MEDLINE, PsycINFO, Web of Science, CRD Database (includes DARE, NHSEED and HTA) and HMIC databases and were searched with those identified keywords. The search strategy for MEDLINE is provided in Appendix 1. The phase of screening for eligibility was conducted by two reviewers independently. In addition, references of selected studies were searched for relevant articles. Any discrepancies were resolved by discussion.

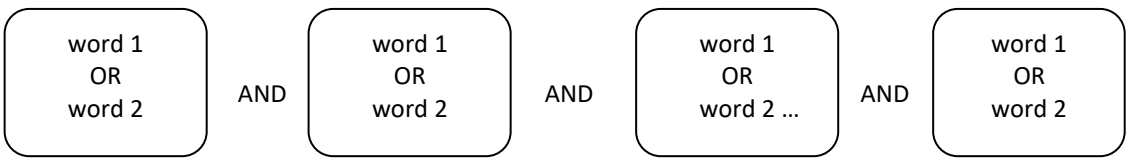


Figure 4.1: Boolean operators' configuration

4.2.3 Data Extraction

A data extraction sheet was produced, covering study design and the databases searched, the number of studies included, main outcomes, inclusion of partners, and some other methodological information. The data extraction tool is presented in Appendix 2. The tool was piloted by the author to ensure accuracy.

4.2.4 Quality Assessment

The Cochrane Handbook (Higgins and Green, 2011) does not suggest any specific tool for the quality assessment of systematic reviews because of the limited research in this area. The checklist proposed by the Centre for Reviews and Dissemination (CRD) was appropriate for this research because it is applicable to different types of systematic reviews (CRD, 2009). The CRD checklist was modified according to the needs of the current study to produce a quality assessment tool. For instance, additional questions about having a protocol, consideration of publication bias and heterogeneity were produced. The final version of checklist is presented in Appendix 3. Quality assessment was done by two reviewers independently and any discrepancies were resolved through discussion.

4.2.5 Identifying the Health Conditions for Inclusion in the Economic Model

The health conditions that should be included in the modelling study were identified based on a causal link analysis and modelling considerations related to the computational difficulties.

4.2.5.1 Causal link analysis

Since the existence of an association would not always warrant a causal link, a causal link analysis was undertaken to inform the modelling study. The widely-accepted nine-item criteria developed by Hill (1965) provide guidance to assess causal relationship:

- Strength: a large association exists.
- Consistency: the impact is observed in different settings by different researchers.
- Specificity: the impact is on a specific condition and amongst a specific population.
- Temporality: exposure precedes disease.
- Plausibility: plausible biological models or mechanisms exist.
- Biological gradient: a dose-response impact exists.
- Coherence: there is laboratory evidence for the causative agent. However, a lack of laboratory evidence would not nullify the epidemiological evidence (Hill 1965).
- Experiment: when the risk is removed, the disease risk decreases.
- Analogy: similar effects are observed for factors other than smoking.

Based on the Hill's criteria, Jones (2015) developed the following classification:

- Potential causal link if there was one systematic review including eight or more studies (group 1)
- Potential causal link if there were more than one systematic review (group 2)
- No causal link if systematic reviews reported conflicting findings (group 3)
- No causal link if one systematic review reported a limited number of studies (<8) which found a relationship (group 4)

There was no justification for the threshold of eight studies used in this classification (Jones 2015), and hence a validity assessment was conducted by reducing the threshold to seven and increasing it to 10 and 12.

In addition to applying the classification by Jones (2015), in this study, the biological gradient was also assessed while the remaining items of the Hill's criteria (coherence, experiment and analogy) were irrelevant because of not including laboratory studies or factors other than smoking. Additionally, the quality assessment and sub-group analyses were considered.

4.2.5.2 Modelling considerations

The ESIP model is a comprehensive model, consisting of one decision tree and two different Markov chains that are linked to each other. Improving this model further would require more components and a significantly high number of parameters. Hence, despite the existence of epidemiological evidence and a causal link, it might not be possible to include all the health outcomes in an economic model. This may be due to the limitations of Markov modelling (e.g. Markovian assumption) or the complex nature of some health conditions (e.g. birth defects). Hence, it was required to

consider these difficulties when identifying the health conditions to be included in the economic model.

4.3 RESULTS

A database search yielded 744 reviews and additional five reviews were found through searching the references of included studies. After eliminating duplicates, 537 reviews remained. Based on abstracts, 64 reviews were selected for further reading; the full-text of one study could not been retrieved despite attempts to contact the author (DiFranza and Lew, 2009). Finally, 63 reviews were included in the analysis. The PRISMA diagram of data selection process is shown in Figure 4.2 (Moher et al., 2009).

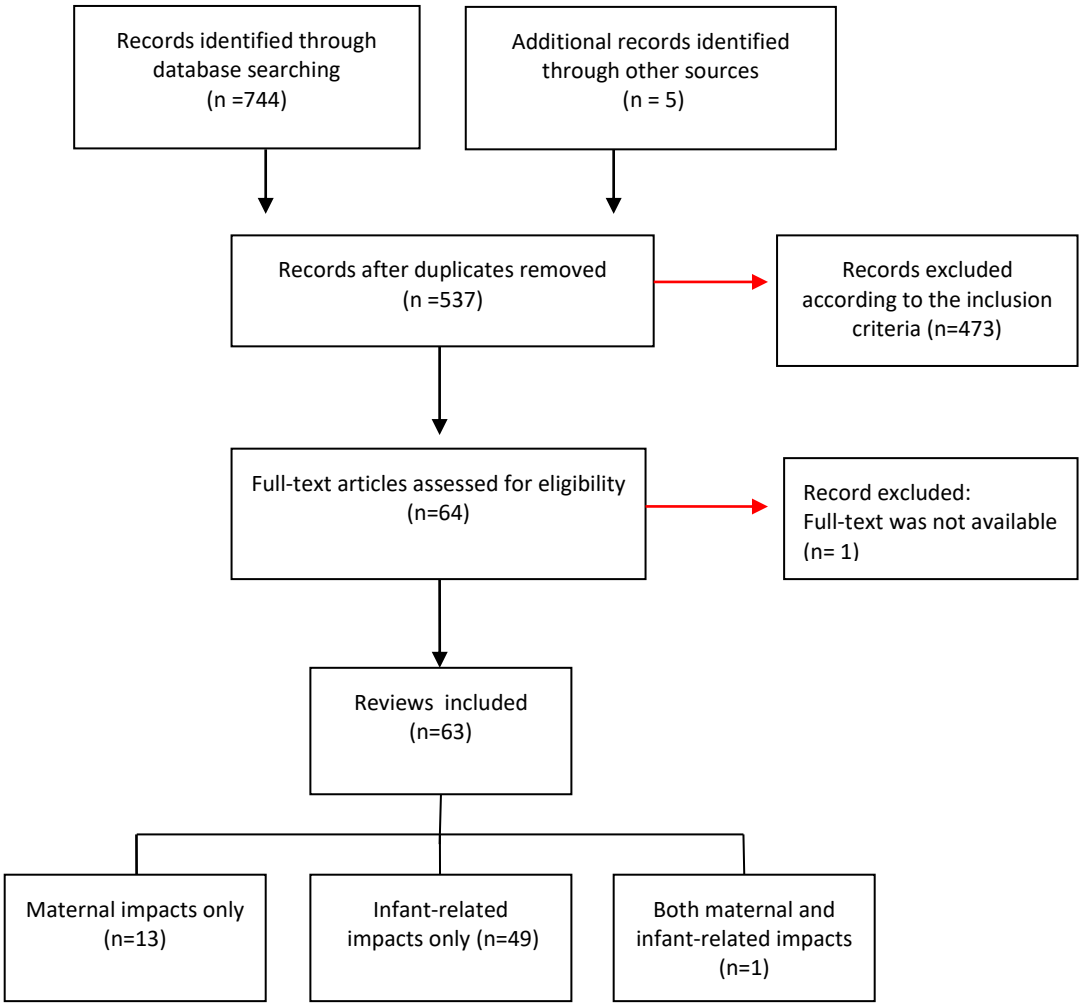


Figure 4.2: PRISMA diagram of study selection

4.3.1 Characteristics of the Included Studies

The main characteristics of the 63 systematic reviews are listed in Appendix 4. The majority of the reviews (n=55) analysed the impact of SDP on a singular condition, whereas seven reviews focussed on more than one condition. Only a small number of reviews (n=13) investigated a health condition related to mothers. Some of the included reviews considered a range of factors (e.g. alcohol, education, and race)

including SDP, which could increase the risk of developing a condition, including 2,495 studies. Among them 1,662 were related to SDP.

The majority of the included systematic reviews conducted meta-analyses (n=53). The studies mostly used odds ratios (n=56) except for a few reviews (n=7) which provided relative risk ratios. As the included reviews did not provide enough information, it was not possible to convert those risk ratios to odds ratios. Hence, the results are reported as they were presented by the authors. Most reviews (n=45) were published in 2010 and later. Hence, the data presented in those reviews were mostly up-to-date.

Although this study aimed not to include any reviews focussed explicitly on LICs, the literature search found no review from LICs. Nevertheless, only 22 of the included reviews covered studies only from HICs. In 27 reviews, included studies were predominantly from HICs. Additionally, in two reviews (Pereira et al., 2017, Tsai et al., 2017) most of the included studies were upper-middle-income countries (UMICs). In one meta-analysis (Weng et al., 2012), studies related to SDP were all from HICs but not all included studies. Unexpectedly, in 12 reviews, the details of the countries of focus were not provided. However, one of them (Kantor et al., 2016) conducted a meta-analysis of the studies from Europe only, and in five of them, the language of included studies was either only English (Latimer et al., 2012, Waylen et al., 2009, Xuan et al., 2016) or a couple of languages (Ankum et al., 1996, Chao et al., 2014) spoken by HICs. In the remaining six (Huang et al., 2007, Huncharek et al., 2002, Ferrante et al., 2014, Little et al., 2004, Tuomisto et al., 2009) there was no indication of focusing on LMICs or HICs , and as a result, they were not excluded.

4.3.2 Quality of the Included Reviews

A quality assessment was undertaken to inform the analysis. The assessment was conducted by two independent reviewers, using an updated version of the checklist provided by CRD. A score was obtained based on the sum of positive answers (*Yes*) except for the statement 4 which was reversely coded and a negative answer (*No*) to this question was counted as one mark. For example, a study with the score of 14 (Nicoletti et al., 2014) had 13 positive answers and one negative answer to question 4. The highest achievable score was 16. Most reviews (n= 24) scored between nine and 11. Some reviews (n=22) achieved a score between 12 and 14 while 17 papers scored between six and eight. Only two reviews (Huang et al., 2007, Tsai et al., 2017) achieved very low scores of 4 and 5. The quality scores of the reviews are shown in Appendix 4. Therefore, most of the included reviews were moderate or high quality reviews according to the criteria used.

Regarding the efforts to minimise bias, most studies did not have a publicly available protocol prepared before conducting the review (n= 56). Study selection was done by two reviewers independently in almost half of the reviews (n=31). The majority of the studies (n=50) assessed publication bias. Additionally, although heterogeneity was measured in all reviews, causes of heterogeneity were not analysed in some (n= 18).

Some of the included reviews (n=29) did not conduct any quality appraisal. Among those conducting a quality assessment, the majority (n= 28) utilised standard instruments. In two reviews (Faiz and Ananth, 2003, Wendland et al., 2008), however, the quality appraisal was based on author's own judgement, and in four reviews

(Hackshaw et al., 2011), it was based on a sub-group analysis. In more than half of the studies (n= 16) that performed a quality assessment, this was conducted by two independent reviewers.

4.3.3 Health Impacts of Maternal SDP on Mothers

The main results of the reviews that investigated the impact of smoking on maternal health outcomes (n=14) are presented in Table 4.2. The findings were consistent, suggesting a significantly increased risk for six conditions amongst women who smoke during pregnancy. Thus, women who smoked during pregnancy had a higher risk of experiencing placental abruption, ectopic pregnancy, miscarriage, placenta previa and preterm premature rupture of the membranes (PPROM). One study also found that the number of asthma exacerbations increased amongst asthmatic pregnant women who smoked (Jayes et al. 2017). The greatest impact was reported for the risk of ectopic pregnancy. Additionally, one review found considerably increased risk of ectopic pregnancy and miscarriage in assisted reproduction (Waylen et al. 2009). On the other hand, pre-eclampsia and hyperemesis gravidarum (pregnancy sickness) were found to be negatively associated with SDP. Hence, the women who smoked whilst pregnant were less likely to experience these two conditions.

Table 4.2 Health Impacts of SDP on mothers

Health Condition	Effect of SDP (OR/RR, CI, number of studies)	Heterogeneity	First Author & Year
Abruptio placenta	OR= 1.9 (95% CI, 1.8-2.0, n=13) OR=1.62 (95% CI 1.46- 1.77, n=8) OR= 1.80 (95% CI, 1.75-1.85, n=27)	Q=41 Not Provided I^2=78%	Ananth 1999 Castles 1999 Shobeiri 2017
Asthma exacerbations	Number of exacerbations increased in smoker or ex-smoker pregnant women in one study.	NA	Jayes 2017
Ectopic pregnancy	OR=2.3 (95% CI, 2.0-2.8, n=6) OR=1.77 (95% CI, 1.31-2.22, n=9) **In assisted reproduction** OR= 15.69 (95% CI 2.87-85.76, n=3)	Not Provided Not Provided Not Provided	Ankum 1996 Castles 1999 Waylen 2009
Hyperemesis gravidarum	OR= 0.40 (95% CI, 0.24-0.56, n=11)	I^2= 94%	Jenabi 2017
Miscarriage	RR= 1.32 (95% CI, 1.21-1.44; n= 25)	Not provided	Pineles 2014
Placenta previa	OR=1.58 (95% CI, 1.04-2.12, n=6) OR= 1.42 (95% CI, 1.30-1.54, n=21) OR =1.6 (95% CI, 1.4, 1.8, n=9)	Not Provided I^2= 63% Not Provided	Castles 1999 Faiz 2003 Shobeiri 2017
PPROM	OR=1.7 (95% CI, 1.18-2.25, n=6)	Not Provided	Castles 1999
Pre-eclampsia	OR= 0.51 (95% CI, 0.38-0.64,n=5) OR= 0.68 (95% CI, 0.57-0.81, n=27) Studies reported up to 50% decrease in the risk. RR= 0.67 (95% CI, 0.60-0.75, n=17)	Not Provided Not Provided NA I^2=92%	Castles 1999 Conde-Agudelo 1999 England 2007 Wei 2015
Spontaneous miscarriage in assisted reproduction	OR=2.65 (95% CI, 1.33-5.30, n=7)	I^2=45%	Waylen 2009

4.3.4 Health Impacts of Maternal SDP on Infants

4.3.4.1 Main findings of the studies with meta-analyses

The meta-analyses investigated 33 infant related conditions; there was a positive association between the risk of 19 conditions and SDP as shown in Table 4.3. The children who were exposed to maternal SDP were at considerably greater risk of LBW,

asthma and obesity, compared to the children who were not exposed to maternal SDP. The increase in the asthma risk was specifically high amongst children aged two and younger (Burke et al., 2012). Increased risks were also reported for preterm birth, birth defects, central nervous system tumors, neuroblastoma, intellectual disability, perinatal death, sudden infant death (SID), lower respiratory infections (LRI) and reduced menarche age.

Studies did not find any statistically significant impact of SDP on 13 conditions, including autism, brain tumors, breast cancer in daughters and testicular cancer in sons although there was a borderline increase in the risks of autism and brain tumors. Studies reported conflicting findings for birth defects, leukaemia and lymphoma since some analyses reported statistically significant increases while the others found no significant increase in risks. The potential reasons of the conflicting findings are presented in Section 4.3.5. Moreover, a protective impact of SDP was reported for skin defects although the number of included studies investigating that association was low (Hackshaw et al., 2011).

Table 4.3: Health impacts of maternal SDP on infants defined in the meta-analyses

Health Condition	Effect of SDP (OR/RR, CI, number of studies)	Heterogeneity	First Author & Year
Asthma	**In children who are 2 & younger,** OR = 1.85 (95% CI, 1.35–2.53, n=5) **In children aged 3 and 4 years** OR=1.30 (95% CI, 0.88–1.92, n=1) **In children aged 5 to 18 years** OR=1.23 (95% CI, 1.12–1.36, n=8)	≤2; I^2=41.9%, 5-18; I^2= 50%	Burke 2012
Atopic dermatitis	OR=0.94 (95% CI, 0.68-1.10, n=UNK)	I^2=74.7%	Kantor 2016
Autism	OR=1.02 (95% CI, 0.93–1.12, n=15) OR=1.02 (95% CI, 0.93-1.13, n=15)	Q=72, I^2=81% I^2=67.3%	Rosen 2015 Tang 2015

Table 4.3: Health impacts of maternal SDP on infants defined in meta-analyses (continued)

Birth defects	**Any type of defect** OR= 1.18 (95%CI, 1.14-1.22, n=188) **Cardiovascular system** OR= 1.11 (95% CI, 1.03-1.19, n=29) **Digestive system** OR= 1.18 (95% CI, 1.07-1.30,n=22) **Musculoskeletal system** OR= 1.27 (95% CI, 1.16-1.39, n=48) **Respiratory system** OR=1.11 (95% CI, 0.93-1.32, n=6) **Urogenital system** OR= 1.04 (95% CI, 0.94-1.12, n=45) **Nervous system** OR=1.09 (95% CI, 0.98-1.21, n=35)	**Any type** I^2=77.2% **CV system** I^2 = 58.7% **Digestive system** I^2 = 21.7% **Musc. system** I^2 = 78.5 **Respiratory system** I^2 = 0.00% **Uregenital system** I^2 = 66.8% **Nervous system** I^2 = 53.5%	Nicoletti 2014
Birth defects (2)	**Any type of defect** OR= 1.01 (95% CI, 0.96-1.07, n=38) **Cardiovascular defects** OR=1.09 (95% CI, 1.02 –1.17, n=25) **Musculoskeletal defects** OR=1.16 (95% CI, 1.05– 1.27, n=25) **Facial defects** OR=1.19 (95% CI, 1.06 –1.35, n=12) **Oral clefts** OR=1.28 (95% CI, 1.20 –1.36, n=38) **Gastrointestinal defects** OR=1.27 (95% CI, 1.18 –1.36, n=35) **Central nervous system** OR= 1.10 (95% CI, 1.01-1.19, n=29) **Respiratory system** OR= 1.11 (95% CI, 0.95-1.30, n=6) **Skin defects** OR=0.82 (95% CI, 0.75– 0.89, n=5)	**Any type** I^2=79% **CV. Defects** I^2= 64% **Musculosketal** I^2 =90% **Facial** I^2=77% **Oral** I^2=43% **Gastrointestinal** I^2 =36% **CNS** I^2=49% **Respiratory** I^2 =0% **Skin** I^2=0%	Hackshaw 2011
Birth defects (3)	**Anorectal malformations** OR=1.03 (95% CI, 0.83-1.29, n=6) **Congenital heart defects** ***Overall*** RR= 1.11 (95% CI, 1.02-1.21, n=19) RR=1.12 (95% CI, 0.99, 1.26, n=10) **Neural tube defects** ***Spina Bifida*** OR=1.55 (95% CI, 1.06-2.26, n=13)	I^2=43% I^2=74% I^2=66% **Spina Bifida** I^2=73 %	Zwink 2011 Lee 2013 Zhang 2017 Wang 2014

Table 4.3: Health impacts of maternal SDP on infants defined in meta-analyses (continued)

Birth defects (4)	**Oral clefts** ***All clefts*** RR=1.34 (95% CI, 1.25-1.44, n=15) ***Cleft palate*** RR=1.22 (95% CI, 1.10-1.35, n=12) **Cleft lips with or without cleft palate(CL/P)** OR= 1.29 (95% CI, 1.18-1.42, n=11) **Cleft Palate (CP)** OR= 1.32 (95% CI,1.10-1.62,n=9) **All clefts** OR=1.40 (95% CI,1.26-1.49, n=11) **Cleft palate only** OR=1.24 (95% CI 1.12-1.38, n=19)	 **All clefts** Not provided **Cleft Palates** Not provided **CL/P** $\chi 2=19.79$, **CP** $\chi 2= 11.26$ **All clefts** $I^2=53.1\%$ **Cleft Palates** $I^2=35.1\%$	Little 2004 Wyszynski 1997 Xuan 2016
Blood Pressure	Difference in blood pressure 0.62 mm Hg, (95% CI, 0.19-1.05)	$I^2= 16\%$	Brion 2008
Bone cancer	OR= 0.79 (95% CI, 0.50-1.26, n=2)	$Q=0.3$, $I^2=0.2$	Rumrich 2016
Brain tumors	OR=1.05 (95% CI, 0.90–1.21, n=12)	Not provided	Huncharek 2002
Breast cancer in daughters	OR= 0.98 (95% CI, 0.86-1.13, n=9)	Q=16.9	Park 2008
Central nervous system tumors	OR = 1.09 (95% CI, 1.02–1.17, n=22)	$I^2=0.3\%$	Rumrich 2016
Germ cell cancer	OR= 0.92 (95% CI, 0.68-1.24, n=4)	Not provided	Rumrich 2016
Gestational diabetes in daughters	OR= 1.03 (99% CI, 0.85-1.25, n=12)	Q=50.14	Wenland 2008
Hepatic tumors	OR= 0.97 (95% CI, 0.70, 1.36, n=3)	$Q=0.9$, $I^2<0$	Rumrich 2016
Intellectual disability	OR=1.10 (95% CI, 1.06-1.15, n= 5)	Not provided	Huang 2016
LBW	Overall: OR= 2 (1.77-2.26, n=30) North America: OR= 1.75 (95% CI, 1.42–2.10, n=7)	$I^2=63\%$ $I^2=63\%$	Pereira 2017
Leukemia	**Childhood leukemia** OR= 0.92 (95% CI, 0.82-1.3, n=21) **Childhood acute lymphoblastic leukemia** OR= 0.99 (95% CI, 0.92-1.06, n=19) **Childhood acute lymphoblastic leukemia** OR= 1.09 (95% CI, 1.01-1.18, n=9)	$I^2=0.5$ $I^2=0.6$ Not provided	Rumrich 2016 Yan 2015
Live birth in assisted reproduction	OR=0.54 (95% CI, 0.30–0.99, n=18)	Not provided	Waylen 2009

Table 4.3: Health impacts of maternal SDP on infants defined in meta-analyses (continued)			
Lower respiratory infections (LRI)	**LRI** RR=1.19 (95% CI, 1.10-1.29, n=11)	I^2=78%	Jayes 2016
	LRI OR=1.24 (95% CI, 1.11-1.38, n=10)	I^2=77%	Jones 2011
	Bronchitis OR=2.44 (95% CI, 1.74-3.40, n=1)	Not Applicable	Jones 2011
Lymphoma, hodgkin lymphoma & non-hodgkin lymphoma	**Lymphoma (L)** OR= 1.21 (95% CI, 1.05-1.34, n=6)	I^2<0	Rumrich 2016
	Lymphoma OR=1.10 (95% CI, 0.96–1.27, n=8)	**L** I^2=0%	Antonopoulos 2011
	Hodgkin lymphoma (HL) OR= 0.90 (95% CI, 0.66–1.21, n=4)	**HL** I^2=0.0%	
	non-Hodgkin lymphoma (NHL) OR= 1.22 (95% CI, 1.03–1.45, n=8)	**NHL** I^2=3%	
Middle ear disease	OR= 1.11 (95% CI, 0.93-1.31, n=6)	I^2=62%	Jones 2012
Neuroblastoma	OR= 1.30 (95% CI, 1.10-1.53, n=5)	Q=0.6, I^2=<0	Rumrich 2016
Overweight and obesity	**Overweight**		
	OR= 1.50 (95% CI, 1.36- 1.65, n=14)	I^2=49%	Oken 2008
	OR=1.47 (95% CI, 1.26-1.73, n=7)	I^2=47%	Weng 2012
	OR= 1.33 (95% CI, 1.23-1.44, n=8)	I^2=0.00%	Riedel 2014
	OR= 1.37 (95% CI, 1.28 to 1.46, n=31)	I^2=45%	Rayfield 2017
	Obesity		
	OR=1.52 (95%CI,1.36–1.70, n=16)	Not provided	Ino 2010
	OR= 1.60 (95% CI, 1.37-1.88, n=4)	I^2=32.47%	Riedel 2014
	OR=1.55 (95% CI 1.40-1.73, n=16)	I^2=24%	Rayfield 2017
Perinatal death & neonatal death	**Perinatal death** RR= 1.33 (95% CI, 1.25-1.41, n= 46)	**Perinatal death** I^2 = 60%	Pineles 2016
	Neonatal death RR= 1.22 (95% CI,1.14-1.30, n= 28)	**Neonatal death** I^2 =39%	
Preterm birth	OR= 1.27 (95% CI, 1.21-1.33, n=20)	Analysed qualitatively	Shah 2000
Reduced menarche age	RR= 1.15 (95% CI, 1.07-1.23, n=3)	I^2=58%	Yermachenko 2015
Renal tumors	OR= 0.95 (95% CI, 0.75-1.22, n=3)	Q=0.9, I^2<0	Rumrich 2016
SID	RR= 2.86 (95% CI, 2.77-2.95, n=47)	χ2=36,	Mitchell 2006
	OR= 2.25 (95% CI, 2.03-2.50, n=23)	I^2=77%	Zhang 2013
Soft tissue tumor	OR= 0.89 (95% CI, 0.71- 1.12, n=5)	Q=0.7, I^2<0	Rumrich 2016
Stillbirth	OR= 1.36 (95% CI, 1.27-1.46, n=4)	I^2=5%	Flenady 2011
	OR=1.55 (95% CI, 1.36-1.78, n=11)	I^2=79%	Marufu 2015
	RR = 1.46 (95% CI, 1.38-1.54, n = 57)	I^2=67%	Pineles 2016
Testicular cancer in sons	OR= 1.0 (95% CI, 0.88-1.12, n=7)	P=0.80	Tuomisto 2009
Wheezing	**Aged 2 or younger** OR= 1.41 (95% CI, 1.20-1.67, n=14)	≤2; I^2 =82%	
	Aged 3 and 4 OR=1.28 (95% CI, 1.14-1.44, n=8)	3-4; I^2=65% 5-18; I^2=21%	Burke 2012
	Aged 5 to 18 OR= 1.52 (95% CI, 1.23-1.87, n=5)		

4.3.4.2 Main findings of the systematic reviews which did not conduct meta-analyses

Systematic reviews without a meta-analysis examined the impact of maternal SDP on 10 infant-related conditions (Table 4.4). Among those only asthma and obesity were covered in studies with meta-analyses as well (Ferrante et al., 2014, Huang et al., 2007), and they reported consistent findings with the meta-analyses (Ino, 2010, Oken et al., 2008, Riedel et al., 2014, Weng et al., 2012, Burke et al., 2012).

One review (Chrestani et al., 2013) reported a positive association between accelerated growth in childhood and maternal smoking pre-pregnancy. In addition, there was evidence showing the negative impact of maternal SDP on visual health, intelligence, academic achievement (Clifford et al., 2012, Fernandes et al., 2015). On the other hand, two reviews (Chao et al., 2014, Jayes et al., 2016) indicated that there was no relationship between maternal SDP, lung function and Tourette syndrome.

Table 4.4: Health impacts of maternal SDP on infants defined in the studies without meta-analyses

Health Condition	Effect of SDP (main outcome)	First Author & Year
Accelerated growth in childhood	OR = 1.29 (95 % CI,0.66–2.49, n=1) OR = 1.46 (95 % CI, 1.04–2.04, n=1)—pre-pregnancy.	Chrestani 2013
Asthma & smoke exposure	Studies showed a positive association between SDP and asthma.	Ferrante 2014
Cognitive parameters of children and young adults	**Poor school performance** ***1–9 cigarettes per day*** aOR= 1.59 (95% CI, 1.55-1.63, n=1); ***≥ 10 cigarettes per day*** aOR=1.92 (95% CI, 1.86-1.98, n=1) 0.26 point yearly reduction in Peabody Individual Achievement Test was observed in one study. Decreased IQ was observed in two studies. **Intellectual impairment** aOR= 1.22 (95% CI, 1.14-1.31, n=1) aRR=1.12 (95% CI, 0.92-1.36, n=1) **Neurodevelopment** 2.5 point deficit (95% CI,− 6.3-1.2, n=1)	Clifford 2012
Lung function in childhood	Current evidence is not sufficient to suggest a significant association between SDP and lung function in children.	Jayes 2016
Disruptive behaviour disorders	aOR=2.1 (95% CI, 1.1-4.1, n=1) aOR= 2.7 (95% CI, 1.1-7.0, n=1) aOR= 4.4 (95% CI, 1.2-15.5, n=1) RR= 2.5 (95% CI, 0.8-7.3, n=1) 15 studies showed a relationship between SDP and increased incidence of attention deficit hyperactivity disorder (ADHD) in the child.	Linnet 2003 Latimer 2012
Overweight and obesity	Eight studies reported positive association, ORs ranging between 1.1 and 2.9.	Huang 2007
Sleep apnea	In infants (1 day-29 weeks) RR= 1.76 (95% CI, 1.17-2.64, n=1)	Jayes 2016
Tourette syndrome (TS) & attention deficit disorder	**TS vs. control** OR = 4.6 (95% CI, 0.45-46.6, n=1) **TS& ADHD vs. control** OR = 8.5 (95% CI , 0.97-75.2, n=1) **TS& ADHD vs. TS** OR = 2.43 (95% CI, 1.23-4.82, n=1) **Presence of OCD** OR = 8.27 (95% CI, 0.87-78.20, n=1)	Chao 2014
Vision difficulties & SDP	SDP is associated to several vision problems according to 24 studies.	Fernandes 2015

4.3.5 Health Conditions with Conflicting Results

Some health conditions were assessed in multiple meta-analyses and there were conflicting results. For instance, an increased risk was reported for having any type of birth defect in one review (Nicoletti et al., 2014), despite the small effect size (OR=1.18, 95% CI, 1.14-1.22) as opposed to an borderline risk (OR=1.01, 95% CI, 0.96-1.07) reported in another (Hackshaw et al., 2011). The main reason behind this difference was the reduced risk of skin defects (OR= 0.82, 95% CI, 0.75-0.89) included in the latter review. All five studies included in this meta-analysis reported a reduced relationship and the heterogeneity was low (P=0.00001, I^2=0%). This protective impact of SDP was not discussed in detail in the review.

Another health condition with mixed findings was leukaemia. One meta-analysis (Rumrich et al., 2016) including 19 observational studies found an insignificant but decreased risk (OR= 0.99, 95% CI, 0.92-1.06), whereas another review (Yan et al., 2015) indicated a significant and increased risk (OR= 1.10, 95% CI, 1.02-1.19) based on 21 studies. The difference can be explained by the different studies included, since there were only five studies included in both. Therefore, the association between SDP and leukaemia is ambiguous.

Similarly, reviews reported conflicting results for lymphoma as well. One meta-analysis (Antonopoulos et al., 2011) found an increased but statistically insignificant risk for any lymphoma based on eight studies (OR= 1.10, 95% CI, 0.96-1.27) although they reported a positive relationship for non-Hodgkin lymphoma (OR=1.22, 95% CI, 1.03-1.45, n=8). Another review (Rumrich et al., 2016) which included six studies reported

an increased and significant risk for any lymphoma (OR= 1.21, 95% CI, 1.05-1.34). Hence, SDP increases the risk of non-Hodgkin lymphoma but for the other types of lymphoma the impact is not yet clear.

4.3.6 Life-time Impacts of Maternal SDP on Infants

The health conditions for infants caused by maternal SDP were observed in different life stages in the included studies. For example, some conditions were measured during infancy while some were measured during adulthood. In some reviews, the participants of the included studies were both infants and adults (Clifford et al., 2012, Oken et al., 2008). Table 4.5 below shows the health conditions based on the life stage when they were assessed.

The conditions measured during the perinatal and neonatal periods included foetal loss, perinatal death, preterm birth, LBW. During infancy, an increase in the risks of SID, LRI, asthma and wheezing was observed. Behavioural problems, asthma, central nervous system tumors and vision difficulties were reported in childhood. Additionally, the reviews reported increased cognitive impairment, overweight and obesity during childhood, adolescence and adulthood.

Table 4.5: Health impacts of maternal SDP on infants by life stages

Life stage	Health implications	References
Perinatal	Foetal loss in assisted reproduction, stillbirth, perinatal death, preterm birth	(Flenady et al., 2011, Marufu et al., 2015, Pineles et al., 2016, Shah and Bracken, 2000)
Neonatal	Accelerated growth, birth defects (i.e. heart defects, oral clefts), LBW, neonatal death, neural tube defects, sleep apnea	(Chrestani et al., 2013, Jayes et al., 2016, Hackshaw et al., 2011, Lee and Lupo, 2013, Nicoletti et al., 2014, Pereira et al., 2017, Pineles et al., 2016, Wyszynski et al., 1997, Wang et al., 2014, Zhang et al., 2017)
Infancy	Asthma, cognitive parameters impairment (decreased IQ, impaired neurodevelopment), intellectual disability, LRI, SID, wheezing	(Burke et al., 2012, Clifford et al., 2012, Jones et al., 2011, Zhang and Wang, 2013)
Childhood	ADHD, accelerated growth, asthma, central nervous system tumours, cognitive parameters impairment (decreased IQ), disruptive behaviour disorders, intellectual disability, neuroblastoma, non-Hodgkin lymphoma, overweight, obesity, vision difficulties, wheezing	(Antonopoulos et al., 2011, Brion et al., 2008, Burke et al., 2012, Clifford et al., 2012, Ino, 2010, Jayes et al., 2016, Latimer et al., 2012, Linnet et al., 2003, Oken et al., 2008, Riedel et al., 2014, Weng et al., 2012)
Adolescence	Asthma, Central nervous system tumours, cognitive parameters impairment (decreased IQ, poor school performance), neuroblastoma, overweight, obesity, reduced menarche age, wheezing	(Burke et al., 2012, Clifford et al., 2012, Ino, 2010, Oken et al., 2008, Riedel et al., 2014, Yermachenko and Dvornyk, 2015)
Adulthood	Central nervous system tumours, cognitive parameters impairment (decreased IQ), overweight, obesity	(Clifford et al., 2012, Ino, 2010, Oken et al., 2008, Riedel et al., 2014)

The reviews included in this study showed that maternal smoking was found to increase the risk of death during the prenatal period, neonatal period and infancy. In addition, SDP was not only associated with short-term conditions but also with some long-term consequences which could have detrimental impacts on individuals' lives.

4.3.7 Dose-response Association

To understand the impact of reducing smoking, it is important to investigate the relationship between the severity of smoking and the risk of any health implications for the infant or the mother. Although a dose-response impact of SDP was reported in 27 reviews (22 related to infant conditions) it was statistically tested only in 17 studies. Among them, four found no significant impact of SDP and their dose-response test showed similar results; hence they are not reported here. The findings of the remaining 13 studies are summarised in Table 4.6 below.

Regarding the thresholds to determine light, moderate and heavy smokers, most studies (Chu P, 2016, Marufu et al., 2015, Nicoletti et al., 2014, Pineles et al., 2016, Rumrich et al., 2016, Zhang and Wang, 2013) chose smoking 10 cigarettes daily (10 cig/day) as a cut-off point to distinguish light smokers from moderate and heavy smokers. In some studies (Nicoletti et al., 2014, Pineles et al., 2016, Rumrich et al., 2016, Shah and Bracken, 2000, Yermachenko and Dvornyk, 2015), both 10 cig/day and 20 cig/day were utilised as the thresholds to distinguish moderate smokers from heavy smokers.

The included reviews showed elevated risks for stillbirth, birth defects, preterm birth and perinatal death as the number of cigarettes increased (Marufu et al., 2015, Nicoletti et al., 2014, Pineles et al., 2016, Shah and Bracken, 2000). On the other hand, the risk of pre-eclampsia reduced as the number of cigarettes consumed increased (Conde-Agudelo et al., 1999). This showed that not only smoking protected against pre-eclampsia but also the risk reduced as the exposure increased.

Additionally, a dose-response relationship was found in four reviews although a pooled estimation was not calculated. They found an increased risk based on the number of cigarettes for placental abruption (Ananth et al., 1999) and for the risk of being overweight amongst infants (Oken et al., 2008) having oral clefts (Wyszynski et al., 1997, Xuan et al., 2016). On the other hand, some reviews (n=6) observed no significant association between the number of cigarettes consumed and the risk of health conditions for the children of smokers although overall they reported a significantly increased risk. These studies covered congenital heart diseases (Lee and Lupo, 2013), central nervous system tumors (Rumrich, 2016), childhood neuroblastoma (Chu P, 2016) and lymphoblastic leukaemia (Yan et al., 2015), and reduced menarche age in daughters (Yermachenko and Dvornyk, 2015).

Table 4.6: Dose-response association between maternal SDP and health conditions

Condition	First	Second and third thresholds	First Author & Year
Birth defects	***9 or less cig/day*** OR=1.19 (95% CI, 1.12-1.26, n=60, I^2=UNK)	***10-19 cig/day*** OR= 1.29 (95% CI, 1.20-1.38, n=60, I^2=UNK) ***20 or more cig/day*** OR= 1.41 (95% CI, 1.30-1.52, n=60, I^2=UNK)	Nicoletti 2014
Central nervous system tumors	***10 or less cig/day*** OR= 1.06 (95% CI, 0.92-1.21, n=14, I^2=0.4%)	***11-20 cig/day*** OR= 1.07 (0.90, 1.27, n=8, I^2<0) ***21 or more cig/day*** OR= 1.01 (95% CI, 0.71-1.44, n=6, I^2<0)	Rumrich 2016
Childhood acute leukemia	***1–10 cigarettes/day vs. 11 or more*** OR=1.03 (95% CI, 0.74-1.42, n=UNK)	***1–20 cigarettes/day vs. 21 or more*** OR=1.11(95% CI, 0.70-1.73, n=UNK)	Yan 2015
Congenital heart defects	***Light smokers*** RR= 0.99 (95% CI, 0.92–1.06, n=UNK)	***Heavy smokers*** RR=1.04 (95% CI, 0.86–1.26, n=UNK)	Lee 2013
Lymphoma	***Increased risk per cigarette*** 0.02 (95%, CI, -0.018- 0.06) ***10 or less cig/day*** OR= 1.28 (95% CI, 0.96-1.69, n=3, I^2<0)	***NA*** ***11 or more cig/day*** OR=1.19 (95% CI, 0.80-1.78, n=2, I^2<0)	Antonopoulos 2011 Rumrich 2016

Table 4.6: Dose-response association between maternal SDP and health condition (continued)

Menarche age	***9 or less cig/day*** Std dif in means -0.094 (95%CI, -0.245-0.57, n=5, I^2 = 71%)	***10-19 cig/day*** Std dif in means -0.080 (0.232- 0.072, n=5 I^2=61%) ***20 or more cig/day*** Dif in means 0.140 (-0.172-0.453, n=3, I^2 =85%)	Yermachenko 2015
Miscarriage	***10 or less cig/day*** RR= 1.08 (95% CI, 0.96-1.21, n= 16, I^2=UNK)	***11–19* cig/day** RR=1.25(95% CI,1.17-1.34, n = 9, I^2=UNK) ***20 or more* cig/day** RR= 1.42 (95% CI,1.19-1.70, n = 11, I^2=UNK)	Pineles 2014
Neonatal death	***10 or less cig/day*** RR= 1.06 (95% CI, 0.90-1.26, n=10, I^2=UNK)	***11-20 cig/day*** RR= 1.30 (95% CI, 1.00-1.68, n=4, I^2=UNK) **21 or more cig/day** RR= 1.31 (95% CI, 1.11-1.55, n=5, I^2=UNK)	Pineles 2016
Neuro-blastoma	***9 or less cig/day*** OR= 0.97 (95% CI, 0.62-1.53, n=3, I^2= 58%)	***10 or more cig/ day*** OR= 1.20 (95% CI, 0.80-1.66, n=3, I^2= 48%)	Chu 2016
Perinatal death	***10 or less cig/day*** RR= 1.17 (95% CI, 1.05-1.31, n=16, I^2=UNK)	***11-20 cig/day*** RR=1.35 (95% CI, 1.18-1.53, n=6, I^2=UNK) **21 or more cig/day** RR= 1.40 (95% CI, 1.32-1.50, n=11, I^2=UNK)	Pineles 2016
Pre-eclampsia	***9 or less cig/day*** Cohort studies: 0.77 (95% CI, 0.73-0.83, n=9)	***10 or more cig/day*** Cohort studies: 0.67 (95% CI, 0.63-0.71, n=9)	Conde-Agudelo 1999
Preterm birth	***9 or less cig/day*** OR= 1.22 (95% CI, 1.13-1.32, n=6, I^2=UNK)	**10-19 cig/day** OR= 1.38 (95% CI, 1.23-1.55, n=6, I^2=UNK) **20 or more cig/day** OR= 1.31 (95% CI, 1.20-1.42, n=5, I^2=UNK)	Shah 2000
SID	***Any smoking*** OR=2.25 (95% CI, 2.03-2.5, n=23, I^2=77)	***10 or more cig/day*** OR=2.30 (1.27-4.18, n=6, I^2=UNK)	Zhang 2013
Stillbirth	***9 or less cig/day*** OR= 1.09 (95% CI, 0.97-1.24, n=6, I^2=0%) ***10 or less cig/day*** RR= 1.10 (95% CI, 0.98-1.24, n=20, I^2=UNK)	***10 or more cig/day*** OR=1.52 (95% CI, 1.30-1.78, n=7, I^2=80) ***11-20 cig/day*** RR= 1.30 (95% CI, 1.22-1.38, n=9, I^2=UNK) **21 or more cig/day** RR= 1.24 (95% CI, 1.03-1.50, n=10, I^2=UNK)	Marufu 2015 Pineles 2016

UNK: Unknown

4.3.8 Second-hand Smoking during Pregnancy

In addition to active smoking, SHS during pregnancy can have health implications for both infants and mothers. Moreover, SHS can also be a confounding factor because of the impacts on infants. As a result, risk ratios can be higher if a partner smokes during pregnancy in addition to the mother, compared to a smoking mother who does not have a partner who smokes (Henceforth is referred to as smoking partner).

Despite the importance of partner's smoking status, it was considered only in ten reviews (Table 4.7); six of them did not assess the impact of passive smoking specific to the pregnancy period. Therefore, those studies showed the impact of passive smoking on various health conditions, but not the impact of having a smoking partner whilst pregnant.

Two reviews investigating the impact of the partner's smoking status during pregnancy found increased risk of SID and delay in mental development (Mitchell 2006, Tsai 2017). Other reviews found no significant impact on brain tumors (Huang et al., 2014) and breast cancer risk in the females (Park et al., 2008).

Table 4.7: Impact of partner smoking

Health Condition	Main Outcome	First Author & Year
Anorectal malformations	**NOT specific to pregnancy** OR=1.53 (95% CI, 1.04-2.26, n=2, P=0.03)	Zwink 2011
Asthma	**NOT specific to pregnancy** ***Paternal smoking*** Aged 3-4; OR=1.34 (95% CI,1.23-1.46, n=1) Aged 5-18; OR=0.98 (95% CI, 0.71-1.36, n=3, I^2=0.0) ***Household smoking*** Aged 2 or younger; OR=1.14 (95% CI, 0.94-1.38 n=3 I^2=1.7) Aged 3-4; OR=1.21 (95% CI, 1.00-1.47, n=5, I^2=72.7) Aged 5-18; OR=1.30 (95% CI, 1.04-1.62, n=6, I^2=37.7)	Burke 2012
Brain tumors	RR= 0.93 (95% CI, 0.85-1.00, n=9, I^2=0%)	Huang 2014
Breast cancer risk in females	OR= 1.0 (95% CI, 0.9-1.1, n=1)	Park 2008
Delayed mental development	OR= 2.36 (95% CI, 1.21-4.59, n=1)	Tsai 2017
LRTI	**NOT specific to pregnancy** ***Paternal smoking*** OR= 1.22 (95% CI, 1.10-1.35, n=21, I^2=62%) ***Household Smoking*** OR= 1.54 (95% CI, 1.40-1.69, n=37, I^2=43%)	Jones 2011
Middle ear disease	**NOT specific to pregnancy** 1.24 (95% CI, 0.98-1.57; n= 12, I^2=87%)	Jones 2012
Miscarriage	1.11 (95% CI, 0.95-1.31, n= 17)	Pineles 2014
Neonatal death	**NOT specific to pregnancy** RR=1.37 (95% CI, 1.04-1.82, n=6, I^2=UNK)	Pineles 2016
Overweight & obesity	**NOT specific to pregnancy** ***Paternal smoking*** ***Overweight*** OR=1.07 (95% CI, 1.00-1.16, n=8, I^2=0.00%) ***Obesity*** OR= 1.23 (95% CI, 1.10-1.38, n=6, I^2=32.47%) ***Household smoking*** ***Overweight*** OR= 1.22 (95% CI, 1.06-1.39, n=3, I^2 =72.14%) ***Obesity*** OR= 1.31 (95% CI, 1.15-1.50, n=3, I^2 =0.00%)	Riedel 2014
Perinatal death	**Any second-hand smoking** RR= 1.42 (95% CI, 1.10-1.85, n=2, I^2=UNK)	Pineles 2016
Stillbirth	**Any second-hand smoking** RR=1.37 (95 % CI, 1.04-1.82, n=6, I^2=UNK)	Pineles 2016
SID	**If mother is non-smoker and father is smoker during pregnancy** RR= 1.49 (95% CI, 1.29-1.77, n=7, $\chi 2$=4.28, p=0.64)	Mitchell 2006
Wheezing	**NOT specific to smoking during pregnancy** ***Paternal smoking*** Aged 5-18; OR=1.39 (95% CI, 1.05-1.85, n=2, I^2=0.0) ***Household smoking*** Aged 2 or younger; OR=1.35 (95% CI, 1.10-1.64, n=10, I^2=64.5) Aged 3-4; OR=1.06 (95% CI, 0.88-1.27, n=4, I^2=54.5) Aged 5-18; OR=1.32 (95% CI, 1.12-1.56 n=5, I^2=1.7)	Burke 2012

4.3.9 Impact of Postnatal Maternal Smoking on Infants

It is important to distinguish the effect of postnatal maternal smoking to estimate the health implications of maternal SDP in the long-term, because postnatal smoking can actually be a confounding factor when considering the impacts of maternal SDP. No review compared the health implications of maternal SDP and postnatal maternal smoking, with postnatal smoking only. Rather, some reviews compared postnatal smoking with not smoking in the postnatal period. Nevertheless, understanding the impact of postnatal smoking is also important because women who smoke during pregnancy would be likely to smoke during the postnatal period as well, considering only around 13% of women who had smoked during pregnancy quit during the year after delivery (HSCI, 2010a).

The included reviews showed that postnatal maternal smoking increased the risks for asthma, LRI, SID and wheezing but not leukaemia, middle ear disease and obesity (Table 4.8). However, it was not clear whether the mothers covered in these studies smoked during whole pregnancy as well or not. One study reported by Oken (2008) found no increase in the prevalence of obesity when mother did not smoke during pregnancy but smoked after the birth.

Table 4.8: Impact of postnatal maternal smoking

Health Condition	Main Outcome	First Author & Year
Asthma	***Aged 2 or younger;*** OR= 2.47 (95% CI, 0.65-9.39, n=2, I^2=3.7%) ***Aged 3-4;*** OR= 1.05 (95% CI, 0.88-1.25, n=4, I^2=0.0%) ***Aged 5-18;*** OR= 1.20 (95% CI, 0.98-1.44, n=8, I^2=65.3%)	Burke 2012
Leukaemia	Three months after pregnancy OR= 0.74 (95% CI, 0.52-1.05, n=4, I^2=0.5)	Rumrich 2016
LRI	OR= 1.58 (95% CI, 1.45-1.73, n=31, I^2=76.5%)	Jones 2011
Middle ear disease	**Bio-chemically verified SHS** OR=1.29 (95% CI, 0.86-1.94, n= 3) **Self-reported SHS** OR, 1.70 (95% CI, 1.29-2.25, n= 17)	Jones 2012
Obesity	Prevalence of obesity OR= 1.6% (95% CI, 0.4%-4.1%, n=1)	Oken 2008
SID	OR = 1.97 (95% CI, 1.77–2.19, n=18, I^2=56.4%)	Zhang 2013
Wheezing	***Aged 2 or younger;*** OR=1.70 (95% CI, 1.24–2.35, n=4, I^2=0.0%) ***Aged 3-4;*** OR= 1.65 (95% CI, 1.20–2.28, n=4, I^2=48.5%) ***Aged 5-18;*** OR= 1.18 (95% CI, 0.99–1.40, n=3, I^2=1.40%) OR=1.93 (95% CI, 1.30-2.83, n=1)	Burke 2012 Tsai 2017

4.3.10 Sub-group Analyses of the Findings in the Included Studies

Some studies conducted sub-group analyses for certain outcomes. This section presents the results of these analyses.

4.3.10.1 Study quality

Study quality may have an impact on the results; for example, publication bias or sample selection bias might confound the findings. Understanding the impact of study quality on the estimated risks, therefore, is important. Of 32 reviews conducted a

quality appraisal of the included observational studies 14 provided information on whether there was a difference in the results between high-quality and low-quality studies (Appendix 5). Their results indicated that high-quality studies reported higher ratios for some conditions (overweight, obesity, placenta previa) as opposed to lower or insignificant ratios for some others (asthma, atopic dermatitis, autism, LBW, miscarriage, stillbirth).

4.3.10.2 Study design

Like study quality, study design may affect the results of a systematic review. The list of studies that provided risk or odds ratios by study type is presented in Appendix 6. Although a sub-group analysis of study design was conducted, the figures for the associations were not provided in four reviews (Hackshaw et al., 2011, Huncharek et al., 2002, Jones et al., 2011). Case-control and cohort studies mostly reported similar findings for most of the conditions. However, for some health conditions (LBW, oral clefts, perinatal death) case-control studies showed greater risks (Little et al., 2004, Pereira et al., 2017, Pineles et al., 2016) while for some others (abruptio placenta, miscarriage and stillbirth) the risks were higher in cohort studies (Ananth et al., 1999, Marufu et al., 2015, Pineles et al., 2014). Only for congenital heart diseases and placenta previa, no statistically significant relationship was found in cohort studies unlike the significant association observed in case-control studies (Faiz and Ananth, 2003, Zhang et al., 2017).

4.3.10.3 Sample size

Since sample size of a study could influence its results, it was important to investigate whether there was a difference in the findings of the reviews based on their sample sizes. In most reviews, studies with a smaller sample sizes found greater effects except for two reviews (Conde-Agudelo et al., 1999, Rumrich et al., 2016, Lee and Lupo, 2013). In another review, studies with a smaller sample sizes were stated to report greater effects than those reported by studies with larger sample sizes, yet the figures were not provided (Oken et al., 2008). The results by sample size are provided in Appendix 7.

4.3.10.4 Other sub-group analyses

There were other aspects of maternal SDP considered in some reviews. Firstly, the impact of ascertainment type, which could be either self-reported or biochemically validated, was investigated in only four reviews. Three of these found similar ratios for prospective and retrospective, biochemical measurement and non-biochemical measurements (Pineles et al., 2016, Jones et al., 2012). One study (Jones et al., 2011) estimated significant increase in the LRI risk amongst children when only the studies with biochemically verified results were included as opposed to the statistically insignificant risk in increase observed in the studies with self-reported measurements.

The second issue to consider is the duration when the infant was exposed to smoking (i.e. pre-pregnancy, first trimester or the whole pregnancy), which was searched in five reviews (Nicoletti et al., 2014, Pineles et al., 2014, Pineles et al., 2016, Rumrich et al.,

2016, Wendland et al., 2008, England and Zhang, 2007). Their results showed no significant difference between women who quit early in pregnancy and those who did not smoke. Therefore, quitting early during pregnancy might eliminate the risk of some health conditions.

In addition, the statistical analysis method may have an impact on the results. This was assessed in only four reviews (Brion et al., 2008, Conde-Agudelo et al., 1999, Rumrich et al., 2016, Pineles et al., 2016). They found similar ratios either using random effects or fixed effects to pool the ratios of the observational studies.

4.3.11 Identifying the Health Conditions for Inclusion in the Economic Model

This umbrella review identified 19 infant related conditions and seven mother-related conditions which had a positive association with SDP and two maternal conditions with a negative correlation with SDP. However, it was needed to evaluate the causal relationship of those conditions with SDP; because an association would not necessarily mean a causal relationship.

4.3.11.1 Causal link analysis

Based on the methodology outlined in Section 4.2.5, a causal link analysis was conducted. The health conditions that were found to have an association with SDP were grouped as shown in Table 4.9.

Table 4.9: Strength of evidence analysis for the identified conditions

Groups	Health conditions
Potential causal link (group 1)	Miscarriage, hyperemesis gravidarum, spontaneous miscarriage in assisted reproduction, lower respiratory infections (LRI), neonatal death and preterm birth.
Potential causal link (group 2)	Abruptio placenta, ectopic pregnancy, placenta previa, pre-eclampsia, birth defects (except skin defect), asthma, low birth weight (LBW), live birth per cycle in assisted reproduction, overweight and obesity, sudden infant death (SID) and stillbirth.
No causal link (group3)	Leukaemia and lymphoma
No causal link (group 4)	Cognitive parameters of children and young adults, disruptive behaviour disorders, intellectual disability, neuroblastoma, PPROM, reduced menarche age, sleep apnea, skin defects and tourette syndrome.

All the conditions in the first and second groups except hyperemesis gravidarum fulfilled the causal link criteria, indicating potential causal link. Yet, there was not sufficient biological explanation to the correlation found between hyperemesis gravidarum and SDP (Verger et al. 2005). Reducing the threshold for the number of studies that was applied by Jones (2015) from eight to seven or increasing it to 10 or 12 did not change the outcome of the causal link analysis.

4.3.11.2 Health conditions to be included in the economic model

The causal link analysis of the health conditions identified by the umbrella review suggested that five maternal conditions and 10 infant-related conditions should be included in the economic model. However, due to the computational requirements and the complex nature of the conditions it was decided not to include neonatal death

and birth defects and consider obesity in the sensitivity analysis rather than in the base-case.

The inclusion of neonatal death (loss of newborns during the first four weeks) would pose difficulties because the ESIP model runs in annual cycles, and there is not enough data for all the model parameters (e.g. smoking behaviour change) to structure the new model in monthly cycles. Additionally, LBW is amongst the causes of neonatal death and the ESIP model assigns a greater mortality risk to infants with LBW, hence incorporating neonatal death would potentially cause overestimating the risk of death during the first year of life (McCormick, 1985, Wilcox and Skjaerven, 1992). Similarly, it would be very challenging to parameterise the impacts on births defects because the various types of defects and their effects on mortality and morbidity.

In addition, due to the controversial nature of the relationship between smoking and obesity, it was decided to include this in the sensitivity analysis not in the base-case analysis. Hence, the base-case analysis included SID and LRI. The conditions to be included in the economic model are presented in Table 4.10.

Table 4.10: Health conditions to be included in the economic model

	Health conditions to be included in the economic model
Maternal	Miscarriage, ectopic pregnancy, abruptio placenta, placenta previa, pre-eclampsia.
Infant-related	Stillbirth, preterm birth, LBW, SID, asthma, LRI, overweight and obesity

4.4 DISCUSSION

This comprehensive umbrella review included 63 reviews which covered 1,662 studies examining the relationship between maternal SDP and 46 health conditions. The review found that SDP increased the risks for 19 infant-related and seven mother-related conditions and reduced risks for two maternal conditions. This included long-term conditions such as obesity and intellectual impairment. Furthermore, some of the reviews reported the impact of paternal smoking during pregnancy and postpartum maternal smoking.

4.4.1 Strengths and Limitations

This is the first umbrella review on the topic and provides the most systematic and comprehensive assessment of the current evidence on the health impacts of SDP. The strengths of the review include in depth consideration of a range of health conditions and the impacts on both mothers and infants. Additionally, the review identifies the evidence related to the impact of SHS by mother's partner during pregnancy, postpartum maternal smoking and the dose-response association.

A systematic approach was followed to assess the causal link between the identified conditions and smoke exposure. Although there is an ongoing debate about causal inference in public health (Glass et al., 2013), the tool developed by Hill (1965) is widely recognised; for example the International Agency for Research on Cancer (IARC) of the World Health Organisation rely on Hill's criteria when defining carcinogenic

hazards to humans (Pearce et al., 2015). In addition to the Hill criteria this study considered the quality of reviews and the findings of sub-group analyses. Hence, the conditions identified by the causal link analysis are very likely to have a causal link with SDP.

Furthermore, a validity test was undertaken to assess whether the threshold of eight studies used by Jones (2015) was appropriate for this study. Increasing the threshold to 10 or 12 or reducing it to seven did not change the study findings. Although increasing the threshold to 12 resulted downgrading the evidence on hyperemesis gravidarum from strong (group 1) to weak (group 4), this did not change the study findings because the evidence on hyperemesis gravidarum did not fulfil the causation criteria.

On the other hand, the study has some limitations to be acknowledged. Firstly, only systematic reviews were included in the review; and as a result, some other health conditions that have been found to be related to maternal SDP were not covered. Some individual studies have indicated the impact of SDP on many other infant-related conditions, such as diabetes (Montgomery and Ekbom, 2002), hypomania (Mackay et al., 2017) and pervasive development disorder (Tran et al., 2013). As these were not assessed in a systematic review, they were not included in this study. In addition, SDP was found to be related to the smoking uptake of the infant later in life (Biederman et al., 2017, Niemela et al., 2016). Moreover, researchers observed that if a grandmother smoked during their pregnancy, their grandchildren were more likely to be diagnosed with autism (Golding et al., 2017). There are also some maternal health conditions

which have been found to be related to smoking whilst pregnant in single studies; e.g. vein thrombosis, myocardial infarction, influenza or pneumonia, bronchitis, gastrointestinal ulcers (Roelands et al., 2009). Therefore, there are some other health impacts of SDP which were not included in this review. However, systematic reviews are considered to be at the highest level of the evidence hierarchy and by focussing on this evidence the current study focussed on health conditions for which a significant amount of research has been conducted.

In addition, the methodological limitations of the observational studies covered in the included reviews should be born in mind when interpreting the results of the current review. For example, long-term implications of SDP were often tested retrospectively by asking mothers of children diagnosed with a condition whether they smoked during pregnancy or not. This indicates three important limitations; first those studies were not designed to compare the children of smoking mothers with the children of non-smoking mothers to see if there were differences in their health. The second one is the reliance on mother's memory and openness, and the last one is the impact of confounding factors. For example, a seven-year-old child with diagnosed asthma could have a mother who smoked during pregnancy in addition to a father who smoked during pregnancy and the postpartum period. It is difficult to disentangle these effects. To minimise the impact of this, the most adjusted estimates were used in this review.

Another consideration was including studies published only in English due to practicalities. Nevertheless, the review was conducted to identify the health impacts of

SDP that should be included in the economic evaluation of UK-based interventions. Hence, studies published in English were of specific relevance.

4.4.2 The Umbrella Review in the Context of Literature

Two previous scoping reviews were conducted to define the health outcomes of SDP although they did not focus on systematic reviews (Godfrey et al., 2010, Jones, 2015). These reviews were not systematic reviews, and the impact of number of cigarettes consumed, partners' smoking and postpartum smoking on infants were not considered. Therefore, the current review is more comprehensive and more systematic than previous studies.

Some of the health conditions covered in this study were also included in the review by Godfrey et al. (2010) but often higher ratios were reported. This might be because they included narrative reviews (Andres and Day, 2000, Salihu and Wilson, 2007, Walsh et al., 1997, Difranza and Lew, 1995) which did not separate maternal SDP and postnatal passive smoke exposure while estimating the summary risk ratios.

The scoping review by Jones (2015) was comprehensive and included 32 health outcomes. That review did not assess the quality of included studies although specific criteria were applied to assess the strength of the evidence. According to the criteria, Jones (2015) suggested that the evidence on the link between obesity and SDP was not strong. However, the current analysis suggested a potential causal link due to the inclusion of two additional systematic reviews (Huang et al., 2007, Riedel et al., 2014).

The biological mechanisms for the impact of smoking on obesity were discussed in detail by Bruin et al. (2010). The evidence from the animal studies showed that nicotine exposure caused increased body weight in the offspring (Oliveira et al., 2009, Somm et al., 2008). Additionally, the association between obesity and SDP was persistent even after controlling the impact of birth weight in some studies (von Kries et al., 2002, Widerøe et al., 2003). Moreover, some recent evidence has shown that LBW did not increase the childhood obesity risk (Qiao et al., 2015). Thus, it was judged that obesity warranted consideration in the economic model. However, since there was no consensus on the causal link due to the potential confounding of lifestyle factors, it was decided to include this condition in the sensitivity analysis not in the base-case (Florath et al., 2014).

Regarding behavioural problems, the current review included two systematic reviews which found a positive association but both reviews failed to fulfil the causal link criteria and scored low in the quality assessment. Likewise, Jones (2015) found the evidence on increased risk of behavioural problems not strong.

4.4.3 Implications for Economic Evaluations of SDP Interventions

The umbrella review suggested that economic evaluations of SDP interventions should consider the following health outcomes: abruptio placenta, ectopic pregnancy, placenta previa, pre-eclampsia, miscarriage, LBW, preterm birth, stillbirth, neonatal death, SID, birth defects, LRI, asthma, overweight and obesity. Furthermore, the severity of smoking and smoke exposure by the partner should be considered.

However, based on the difficulty of incorporating birth defects and neonatal deaths into a Markov model, it was decided not to include these conditions in the new economic model.

This study followed a robust and systematic way to identify the health outcomes that warrant including in the economic evaluation of SDP interventions. This is an important contribution because the previous economic evaluations focussed on a limited number of health conditions, and often there was no clear methodology regarding the identification of health conditions (Jones et al., 2015).

The health conditions included in the ESIP model were identified based on a scoping review and a causal link analysis (Jones 2015), following a more systematic approach than the previous economic evaluations. However, there was no clear justification for the omission of some conditions. For example, although their methodology suggested that no condition would be excluded on the basis of incidence; birth defects and SID were excluded due to rarity. The current study adopted a more transparent approach when deciding whether a specific condition should be included in the economic model.

4.4.4 Gaps in the Literature

This review has identified important gaps in the literature around the protective impact of SDP. Some reviews found smoking could have a protective impact on pre-eclampsia, hyperemesis gravidarum and skin defects in the infants. The protective impact on pre-eclampsia could be explained by the reduction in the anti-angiogenic proteins which prevent the growth of new blood vessel cells (Jeyabalan et al., 2008).

However, there was evidence showing that smoking worsens birth outcomes among women who experience pre-eclampsia (Cnattingius et al., 1997, Pipkin, 2008). In addition, some studies found that women over 35 and those who had hypertension were more likely to develop pre-eclampsia (Chang et al., 2014, Chappell et al., 2008). Hence the relationship between SDP and pre-eclampsia is yet to be fully explained. Regarding the protective impact of SDP on hyperemesis gravidarum there was no clinical explanation. Similarly, the negative association found between skin defects on the infants and SDP could not be explained biologically. Thus, further research is needed to investigate the physiological mechanisms behind those associations.

Further literature gaps were identified around the impact of severity of smoking. Although the severity of smoking has potentially a great importance for estimating the effects of SDP fully, many studies did not investigate it. Some reviews indicated that for some conditions heavy smokers have a higher risk compared to moderate and light smokers. However, there were also some counter-intuitive results reported (Shah and Bracken, 2000). This may have been affected by differing definitions of light, moderate and heavy smokers. Similarly, regarding the dose-response impact of SDP on stillbirth, Pineles et al. (2016) reported that the proportion of pregnant women who were heavy smokers was very low and their rare characteristics could be the cause of risk ratios that were lower than those of moderate smokers. Therefore, more research is needed to clearly understand the impact of each additional cigarette consumed on health outcomes.

Additionally, only two studies assessed the impact of smoke exposure by partner during pregnancy despite possible confounding effects. Hence more research is needed to understand whether having a smoking partner during pregnancy increases the health condition risks caused by SDP.

Moreover, only three meta-analyses investigated the difference between women who quit smoking just before or during the early stages of pregnancy and women who smoked throughout pregnancy (Pineles et al., 2016, Rumrich et al., 2016, Pineles et al., 2014). There was no significant increase in miscarriage, stillbirth and central nervous system tumors if mothers quit early in pregnancy, compared with non-smokers (Pineles et al., 2014, Pineles et al., 2016, Rumrich et al., 2016). This was consistent with the evidence from other studies showing the benefits of quitting during the first trimester (Mezzacappa et al., 2011, Niemela et al., 2016).

4.5 CONCLUSION

This study has shown that smoking during pregnancy and the postpartum period has significant health consequences on mothers and infants that should be included in economic evaluations of SDP interventions, involving decision-analytic model. Some studies reported a protective impact of SDP on pre-eclampsia, hyperemesis gravidarum and skin defects in the infants. There was limited evidence around the impact of severity of smoking and partner smoking on health outcomes.

4.6 CHAPTER SUMMARY

This chapter presented the findings of an umbrella review which identified the health outcomes of SDP and postnatal maternal smoking on mothers and infants. The review included 63 systematic reviews which suggested increased risks for 19 infant-related and seven mother-related conditions and reduced risks for two maternal conditions. Amongst those, the evidence on 10 infant-related and five mother-related conditions fulfilled the causal link criteria. Based on the computational practicalities and the prevalence of the conditions, it was decided to include eight infant-related and five maternal conditions in the economic evaluation of SDP interventions. The next chapter presents the development of the economic model for evaluating SDP interventions.

CHAPTER 5: DEVELOPING AN ECONOMIC MODEL FOR SMOKING DURING PREGNANCY INTERVENTIONS

5.1 INTRODUCTION

As the umbrella review in Chapter 4 has demonstrated, SDP has long-term health outcomes that should be captured in an economic evaluation of interventions to tackle SDP. A Markov model, therefore, is needed to estimate the long-term impacts of SDP interventions and to identify the key characteristics of optimum smoking cessation interventions for pregnant women. As discussed in Section 3.8.1, it was decided to build a new model by improving the ESIP model developed by Jones et al. (2018).

This chapter explains the development of the Economic impacts of Smoking In Pregnancy-Household (ESIP.H) model. The chapter starts with the objectives of the modelling work. Then, the model is presented in five sections; the within pregnancy component (WPC), the mother lifetime component (MLC), the partner lifetime component (PLC), the offspring childhood component (OCC) and the offspring adulthood component (OAC). Next, the model outputs and the construction of the model in Excel are explained. Finally, in the discussion section, the differences

between the ESIP.H and ESIP models and the strengths and limitations of the model are analysed.

5.1.1 Objectives of the Economic Model

The study aimed to build a comprehensive model to conduct a more accurate evaluation of SDP interventions and explore the characteristics of 'optimum' smoking cessation interventions for pregnant women.

5.1.2 Identifying the Evidence on the Impacts of SDP

Due to limited evidence and computational difficulties, it was possible to address only some of the limitations of the ESIP model through the inclusion of some additional health conditions, the impact of former smoking, partner's smoking, the severity of smoking, using biochemically verified postpartum relapse rates.

Table 5.1 presents the evidence related to the health conditions to be included in the new model.

Table 5.1: Health conditions to be included in the new ESIP model

Health Condition	Impact of SDP	Source
LRI	OR=1.24 (95% CI, 1.11-1.38, 10 studies) RR=1.19 (95% CI, 1.10-1.29, 11 studies)	Jones 2011 Jayes 2016
SID	RR= 2.86 (95% CI, 2.77-2.95, 47 studies) OR= 2.25 (95% CI, 2.03-2.50, 23 studies)	Mitchell 2006 Zhang 2013
Obesity (Sensitivity analysis)	OR=1.52 (95%CI,1.36–1.70, 16 studies) OR= 1.60 (95% CI, 1.37-1.88, 4 studies) OR=1.55 (95% CI, 1.40-1.73, 16 studies)	Ino 2010 Riedel 2014 Rayfield 2017

To address the remaining limitations, the findings of the umbrella review were used. However, further review of the literature was needed if there was no relevant evidence in the umbrella review. In these cases, the following steps were followed:

- checking the references of the systematic reviews included in the umbrella review,
- conducting brief literature searches for meta-analyses and
- checking the references of the PhD thesis by Jones (2015).

These steps were not followed in full for every condition; because if a recent meta-analysis was identified in the early steps, the search was ended. However, if there were no meta-analyses all steps were followed until identifying the studies investigated the relationships that were being searched for.

5.2 DEVELOPING THE ECONOMIC IMPACTS OF SMOKING IN PREGNANCY-HOUSEHOLD (ESIP.H) MODEL

As discussed above, it was decided to improve the ESIP model and develop ESIP.H by including additional health conditions, a household approach and the severity of smoking as well as by introducing a feature to allow the user to enter postpartum relapse rates. This section identifies the structure of ESIP.H and explains how it was developed. Before developing the ESIP.H model, some errors in ESIP were corrected and a list of those corrections is presented in Appendix 8.

ESIP.H includes five components; the within-pregnancy component, the mother lifetime component (MLC), the partner lifetime component (PLC), the offspring childhood component (OCC), and the offspring adulthood component (OAC). Figure 5.1 below provides a simplified illustration of the model.

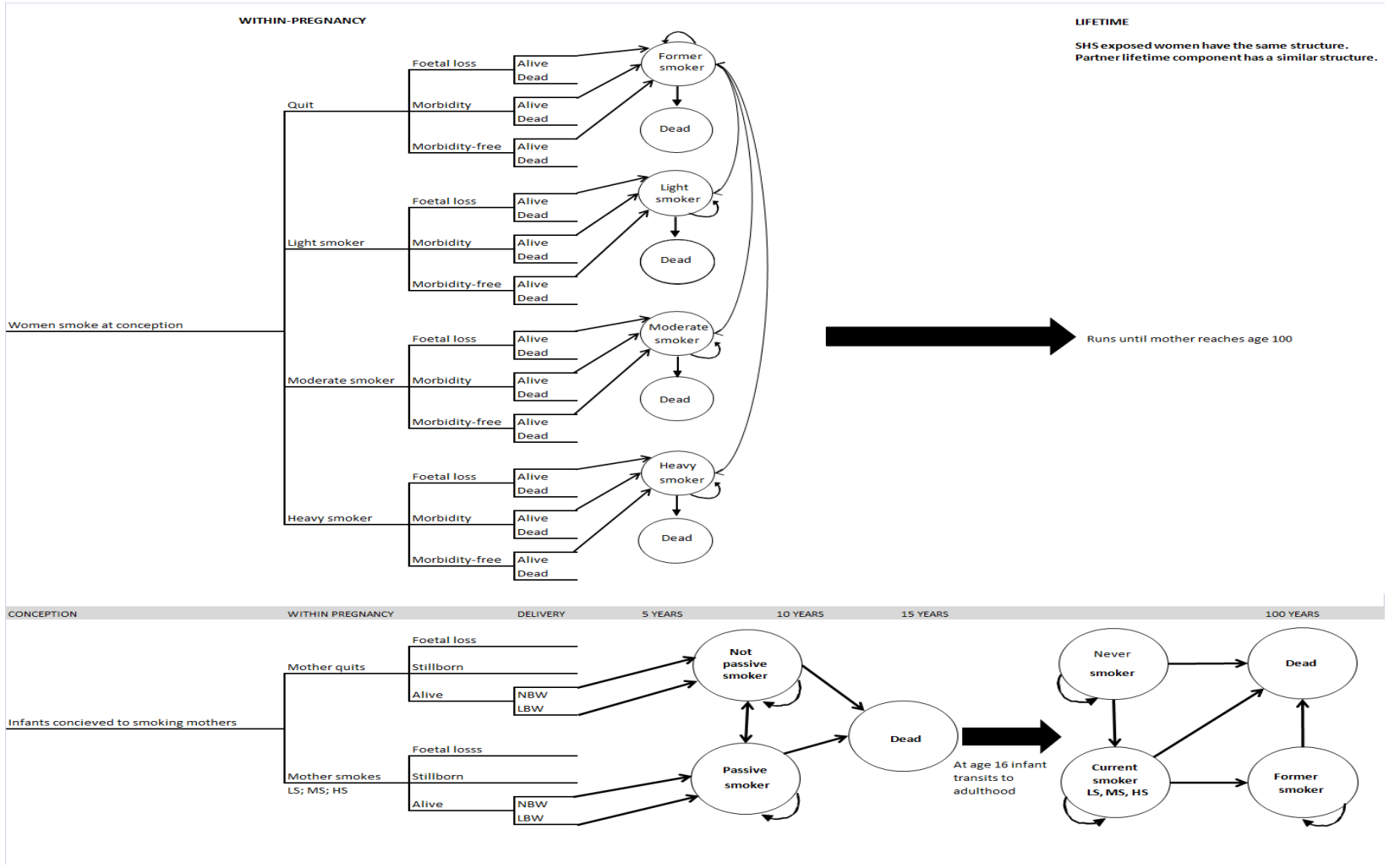


Figure 5.1: Simplified illustration of the model

5.2.1 Within-Pregnancy Component

5.2.1.1 Model Structure

In the within-pregnancy component (WPC), the ESIP model used a decision tree to estimate the health and cost impacts of SDP, and Jones (2015) provided three main reasons for this: i. pregnancy is a short period, ii. the end of pregnancy is accepted as time zero in lifetime models, iii. decision tree would be the simplest option. The ESIP.H model used a decision tree for the within-pregnancy component for the same reasons. However, due to inclusion of the severity of smoking and SHS exposure during pregnancy, the form of decision tree was different in ESIP.H. This section explains the structure of the decision tree and the estimations undertaken to derive the parameters for the model.

ESIP grouped women as former smokers and smokers at the beginning of the decision tree. In contrast, ESIP.H groups women as SHS-exposed and SHS-unexposed. Then, each group is separated into four categories according to their own smoking behaviour at delivery; former, light, moderate, and heavy smokers as shown in Figure 5.2.

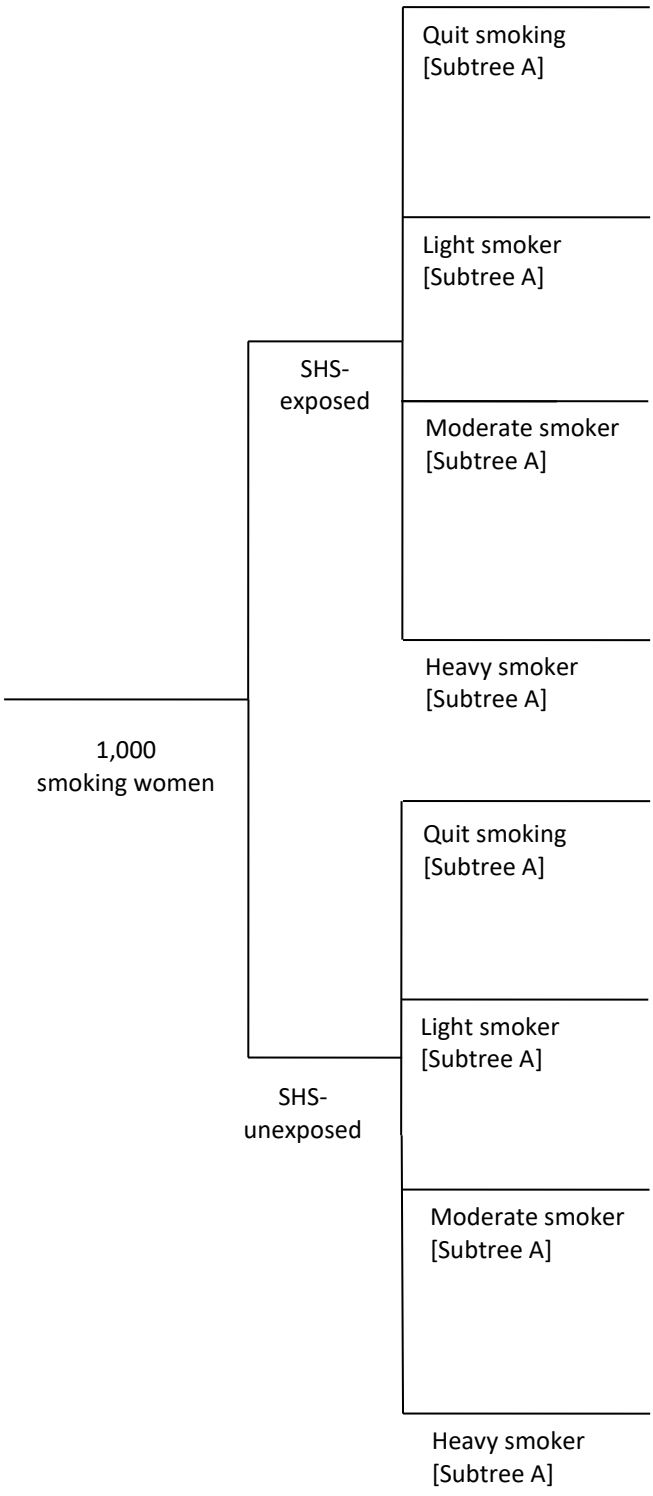


Figure 5.2: Starting the decision tree

The remaining branches of the decision tree are then repeated for all eight groups of women as illustrated in Figure 5.3.

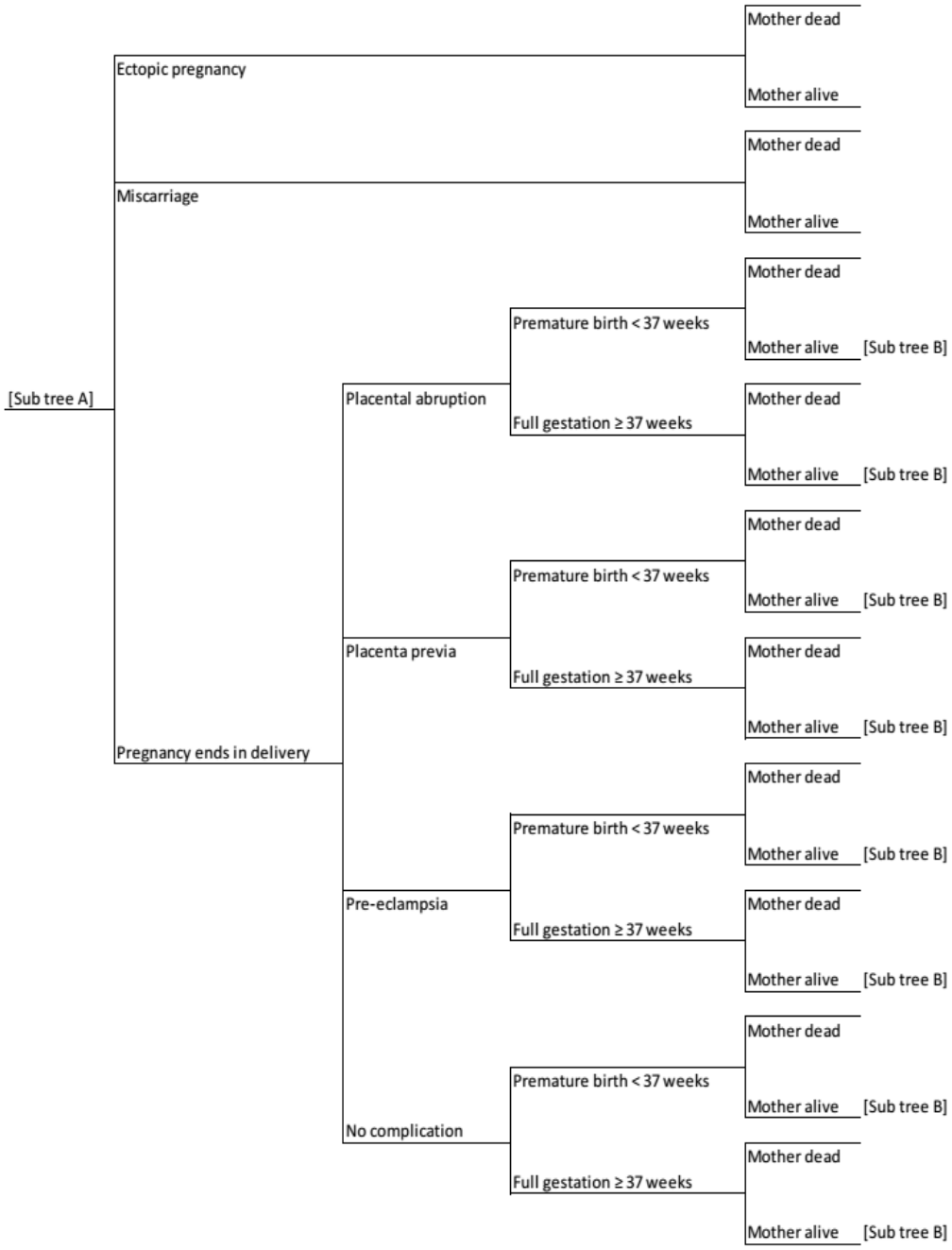


Figure 5.3: Within pregnancy component decision tree structure (Jones, 2015: 156)

The mother component is directly linked to the infant-related health outcomes such that children born to women in every branch (Sub-tree B in Figure 5.4) has probability of LBW and/or stillbirth.

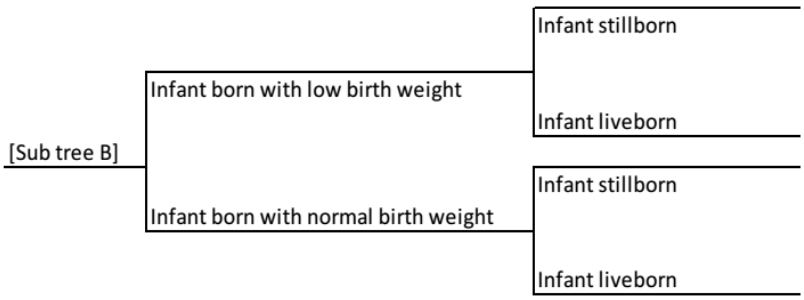


Figure 5.4: The final branch of decision tree (Jones, 2015: 157)

5.2.1.2 Model Parameters

5.2.1.2.1 Smoking patterns and second-hand smoke exposure at delivery

In the ESIP.H the model, second-hand smoking (SHS) and the number of cigarettes consumed by mothers were incorporated. Hence, identifying the proportion of pregnant women exposed to SHS during pregnancy, quit rates at delivery and smoking patterns for the SHS exposed and unexposed was required.

According to the IFS data (2010) the proportion of smoking pregnant women who were exposed to SHS by their partner was 0.68, which was similar to the result of a recent trial conducted in England (Cooper et al., 2017). Additionally, Ratner et al. (1999) reported that 5% of smoking partners quit by delivery. Therefore, the proportion of women exposed to SHS at delivery was estimated at 0.65 (0.68 - 0.68 X 0.05).

Regarding quit rates at delivery in the IFS data, 0.55 of SHS-exposed women quit at delivery, and the corresponding figure was 0.68 for those not exposed to SHS (Fitzpatrick et al., 2016). However, those proportions were deemed too high compared to the figure (0.09) reported by Jones (2015), which was estimated based on trials. This was because the IFS data relied on self-reported abstinence rates, whereas in trials, biological verification was sought, indicating the figure from trials was more reliable. In addition, Riaz et al. (2018) estimated that pregnant women who lived with a smoking partner or other household member were less likely to quit smoking in a meta-analysis of 14 trials (OR= 0.42, 95% CI, 0.35-0.50). Hence, the quit probability (0.09) was adjusted to estimate the SHS contingent quit probability at delivery (0.06 and 0.14), using the below formula based on the study by Flack et al. (2007).

$$Odds\ (Quit|SHSunexposed) = \frac{Probability\ _{SHSunexposed}}{1 - Probability\ _{SHSunexposed}}$$

$$Odds\ (Quit|SHSunexposed) =$$

$$\frac{Odds\ (Quit|Smoking\ pregnant\ women)}{\left(OR_{SHSexposed} \times Prevalence_{SHSexposed}\right) + \left(Prevalence_{SHSunexposed}\ \right)}$$

$$Odds\ (Quit|SHSexposed) = Odds_{SHSunexposed} \times OR_{SHSexposed}$$

$$Probability\ (Quit|SHSexposed) = \frac{Odds_{SHSexposed}}{1 + Odds_{SHSexposed}}$$

Smoking women were grouped according to the severity of smoking based on the proportions (0.4, 0.32 and 0.28 for light, moderate and heavy smokers respectively) obtained from the cohort study in England (Cooper et al., 2017). The estimated probabilities are provided in Table 5.2.

Table 5.2: Smoking patterns at delivery by SHS exposure

SHS exposure	Abstinent at delivery	Light Smoker	Moderate Smoker	Heavy Smoker
YES	0.06	0.38	0.30	0.26
NO	0.14	0.35	0.27	0.24

5.2.1.2.2 Risk of foetal loss before delivery in the general population

Jones (2015) estimated the number of pregnancies that did not end up with delivery by using the Hospital Episode Statistics for England between 2006 and 2013. For the ESIP.H model this was updated by using the data for the years 2006 to 2018 (HSCI, 2018). According to this data, the risk of miscarriage reduced slightly from (0.0606 to 0.0585) while ectopic pregnancy remained unchanged (Table 5.3).

Table 5.3: Number of all pregnancies that did not end in delivery (foetal loss)

Year	Delivery	Miscarriage	Ectopic pregnancy	Total
2006-07	629,207	43,155	9,941	682,303
2007-08	649,837	43,870	10,352	704,059
2008-09	652,638	43,390	10,348	706,376
2009-10	652,377	45,232	10,635	708,244
2010-11	668,195	43,005	11,157	722,357
2011-12	668,936	42,538	11,294	722,768
2012-13	671,255	39,800	11,199	722,254
2013-14	646,904	38,869	10,436	696,209
2014-15	636,643	38,377	10,321	685,341
2015-16	648,107	38,349	10,542	696,998
2016-17	636,401	37,814	10,470	684,685
2017-18	626,203	37,398	10,459	674,060
Total	**7,786,703**	**491,797**	**127,154**	**8,405,654**
Probability*		**0.0585**	**0.0151**	

Source: HES NHS Maternity Statistics 2017-2018

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

5.2.1.2.3 Population risks of delivery complications

There were three pregnancy-related conditions included in the model; placental abruption, placenta previa and pre-eclampsia. Similar to the risk of foetal loss, the risk of delivery complications was updated, using the most recent data available (HSCI, 2018). The estimated prevalence of pregnancy complications are provided in Table 5.4, which were similar to the estimations by Jones (2015).

Table 5.4: Number of all pregnancies that had a delivery complication

Year	Placental abruption	Placenta previa	Pre-eclampsia	No complication*
2006-07†	2,183	3,540	11,119	612,365
2007-08†	2,375	3,758	11,718	631,986
2008-09†	2,422	3,985	12,120	634,111
2009-10†	2,506	4,093	12,778	633,000
2010-11†	2,458	4,368	13,017	648,352
2011-12†	2,491	4,446	12,598	649,401
2012-13‡	2,666	4,420	13,211	650,958
2013-14‡	2,690	4,527	12,779	626,908
2014-15‡	2,643	4,341	12,787	616,872
2015-16‡	2,810	4,397	13,448	627,452
2016-17‡	2,894	4,579	13,716	615,212
2017-18‡	2,865	4,397	14,352	604,589
Total	**31,003**	**50,851**	**153,643**	**7,551,206**
Probability	**0.0039**	**0.0065**	**0.0197**	**0.8761**

†Source: Table 22 NHS Maternity Statistics, 2018 ‡ Source: Table 7.d NHS Maternity Statistics, 2018
* Number of delivery episodes minus deliveries with complications

5.2.1.2.4 Estimating smoking contingent probabilities for pregnancy-related conditions

To estimate the probability of a mother experiencing pregnancy complications depending on the number of cigarettes consumed and SHS exposure, risk ratios reported by the studies identified based on the criteria in Section 5.1.2 were used. If there were more than one study, the following were applied to choose between them:

- More current and comprehensive meta-analysis preferred to less comprehensive and older meta-analysis.
- Meta-analysis preferred to observational studies.
- Observational studies conducted in HICs preferred to observational studies in LMICs.
- Studies with bigger sample preferred to small sample studies.

An example of this was the choice between two meta-analyses identified by the umbrella review which investigated the association between abruptio placenta and SDP. One of those (Shobeiri et al., 2017) was more up to date and included more studies (n=27) compared to the other (n=8) (Castles et al., 1999). Therefore, the odds ratios reported in the most current and comprehensive review (Shobeiri et al. 2017) was utilised in the estimations. However, none of these studies analysed the impact of number of cigarettes consumed. Hence, after following the steps outlined in section 5.1.2 some observational studies were identified (Ananth et al., 1999, Aliyu et al., 2011, Cnattingius et al., 1997, Kyrklund-Blomberg et al., 2001, Raymond and Mills, 1993, Williams et al., 1991). Among those one study (Aliyu et al., 2011) was selected based on setting and sample size, and its findings were used in the calculations conducted for deriving model parameters.

It is important to note that the definitions of light, moderate and heavy smokers were not the same in all studies. For instance, one study identified light smoking as consuming 10 cigarettes or less daily while another one defined it as smoking less than 10 cigarettes daily. Cooper et al. (2017), on the other hand, classified smoking groups differently (≤5, 6-10, ≥11). The risk ratios were used for the appropriate group regardless of the number of cigarettes, e.g. risk ratios for the women with the lowest

amount of consumption were used for light smokers. Table 5.5 below provides a list of risk ratios for different exposure categories.

Table 5.5: Impact of smoking in pregnancy on the risk of developing the included conditions by the severity of smoking

Condition	Former smoker	Light smoker	Moderate smoker	Heavy smoker	Source
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	
Ectopic pregnancy	1.5 (1.1-2.2)	1.6 (1.2-2.1)	2.9 (3.2- 3.7)	3.7 (2.8-5.0)	Bouyer 2003
Miscarriage (RR)	0.9 (0.7-1.2)	1.1 (0.9-1.2)	1.2 (1.2-1.3)	1.3 (1.2-1.7)	Pineles 2014
Placental abruption	-	1.5 (1.4-1.6)	1.6 (1.5-1.7)	1.9 (1.7-2.0)	Aliyu 2011
Placenta previa	-	1.4 (1.2-1.5)	1.4 (1.3-1.6)	1.7 (1.5-1.9)	Aliyu 2011
Pre-eclampsia	-	0.8 (0.7-0.8)	0.7 (0.6-0.7)	-	Conde-Agudelo 1999

Regarding the impact of being a former smoker, there was no estimation for placental abruption and placenta previa. Therefore, for those conditions, it was assumed that the risks for former smokers were the same as never smokers.

The following formula was applied to estimate probabilities in never smokers after adjusting it to include former smokers too (Flack et al., 2007):

$$Prevalence\ (Morbidity|Never\ smoker) =$$

$$\frac{P(Morbidity|Population)}{P_{NS} + (P_{LS} \times RR_{LS}) + (P_{MS} \times RR_{MS}) + (P_{HS} \times RR_{HS}) + (P_{FS} \times RR_{FS})}$$

where NS, LS, MS, HS, and FS stand for never smokers, light smokers, moderate smokers, heavy smokers and former smokers, respectively.

According to the IFS data (2010) 21% of non-smoking women lived with a smoking partner during pregnancy. That was used as a proxy for SHS exposure in non-smoking women, and to estimate the risk in never smokers who were not exposed to SHS the following was applied:

$$Prevalence\left(Morbidity\Big|_{not\ exposed\ to\ SHS}^{NS}\right) = \frac{P(Morbidity|NS\ women)}{P_{\substack{Not\ exposed\ to \\ SHS}} + \left(P_{Exposed\ to\ SHS} \times RR_{SHS\ exposed}\right)}$$

5.2.1.2.5 Estimating morbidity probabilities based on SHS exposure during pregnancy

It was assumed that SHS during pregnancy had no additional impact on active smokers because no study was identified showing this relationship. Studies reported that SHS significantly increased the risk of miscarriage and abruption in non-smoking women (Table 5.6). However, applying those risks would result with higher risks for SHS-exposed non-smoking women compared to light smokers. Therefore, taking a conservative approach, the model assumed the increase in risks among SHS-exposed women would be the same as light smokers. For the other conditions, it was assumed that SHS had no impact because one study showed that partners' smoking did not have any impact on pre-eclampsia (Parazzini et al. 2003) and no evidence was identified for ectopic pregnancy and placenta previa.

Table 5.6: Increased risks for pregnancy complications for women exposed to SHS during pregnancy

Condition	Risks for SHS exposed (Source)	Risks for light smokers (Source)
Miscarriage	RR=1.13 (95% CI, 0.91- 1.42) (Pineles et al. 2014)	RR=1.08 (0.96-1.21) (Pineles et al. 2014)
Placental abruption	OR= 2.20 (95% CI, 1.30-3.60) (Tikkanen 2006)	OR= 1.54 (1.43-165) (Aliyu 2011)

Probabilities for women who were SHS-exposed and for those not SHS-exposed were estimated by applying the following.

$$\text{Probability for SHS exposed FS} = \frac{\text{Odds in FS} \times \text{OR for SHS exposed}}{(1 + \text{Odds in FS} \times \text{OR for SHS exposed})}$$

5.2.1.2.6 Worked example for placental abruption

The odds of placental abruption in all women regardless of their smoking status are:

$$Odds\ (placental\ abruption\ |all\ women) = \frac{\rho}{1-\rho} = \frac{0.0398}{1-0.0398} = 0.0040$$

The recent data suggests that around 11% of all pregnant women were smokers at the time of delivery and 9% of them stopped smoking upon discovering they were pregnant, the remaining 80% were either never smokers or those who quit smoking prior to becoming pregnant (HSCI, 2019, HSCI, 2010a). Based on the study by Cooper et al (2017), at the time of delivery, 40% were light smokers while 32% were moderate and 28% were heavy smokers.

Aliyu et al. (2003) reported the odds ratios for ectopic pregnancy among former, light, moderate and heavy smokers as 1.0, 1.5, 1.6 and 1.9 respectively. Hence, the odds for a non-smoker are:

$$\frac{0.004}{0.80 + (1.5 \times 0.40) + (1.6 \times 0.32) + (1.9 \times 0.28) + (0.09 \times 1)} = 0.0037$$

The proportion exposed to SHS amongst non-smoking women was 21% (IFS 2010) and the OR for SHS exposed was estimated at 1.5 (Aliyu et al. 2011). Hence, the odds for non-smoking women who are not exposed to SHS would be:

$$\frac{0.0037}{0.79 + (1.5 \times 0.21) + 0.89} = 0.0033$$

Thus, the odds for a former smoker developing placental abruption are:

$$0.0033 \times 1 = 0.0033$$

The probability then would be:

$$\frac{0.0033}{1 + 0.0033} = 0.0033$$

This process was repeated for all conditions and the results are provided below in Table 5.7.

Table 5.7: Probabilities of pregnancy complications contingent on the severity of smoking

SHS	Condition	Former smoker	Light smoker	Mod. smoker	Heavy smoker
Yes	Ectopic pregnancy	0.0185	0.0197	0.0352	0.0445
	Miscarriage	0.0525	0.0615	0.0712	0.0724
	Placental abruption	0.0051	0.0051	0.0054	0.0062
	Placenta previa	0.0062	0.0085	0.0089	0.0104
	Pre-eclampsia	0.0204	0.0158	0.0137	0.0137
No	Ectopic pregnancy	0.0185	0.0197	0.0352	0.0445
	Miscarriage	0.0513	0.0615	0.0712	0.0724
	Placental abruption	0.0033	0.0051	0.0054	0.0062
	Placenta previa	0.0062	0.0085	0.0089	0.0104
	Pre-eclampsia	0.0204	0.0158	0.0137	0.0137

5.2.1.2.7 Premature birth

To derive the probability of premature birth for each pregnancy complication, the ONS data on gestational length for 2012-2018 was used (HSCI, 2018). The estimated probabilities are provided in Table 5.8.

Table 5.8: Number and risk of premature birth by birth complication

Year	Total preterm	Placental abruption	Placenta previa	Pre-eclampsia	No complication
2012-13	46,642	1,074	1,163	3,618	40,787
2013-14	41,631	1,018	1,174	3,463	35,976
2014-15	44,138	1,018	1,133	3,432	38,555
2015-16	43,760	1,045	1,105	3,473	38,137
2016-17	42,354	1,092	1,146	3,351	36,765
2017-18	42,949	1,086	1,152	2,601	38,110
Total	**261,474**	**6,333**	**6,873**	**19,938**	**228,330**
Probability		**0.3822**	**0.2578**	**0.2483**	**0.0610**

Source: Table 7.d NHS Maternity Statistics for England (relevant year)

To determine the probability of premature birth by smoking status, risk ratios estimated by Shah et al. (2000) were applied (OR=1.22, 95% CI 1.13-1.32 for light and moderate smokers and OR=1.31, 95% CI 1.20-1.42 for heavy smokers). Regarding the SHS exposure, findings of a recent meta-analysis by Cui et al. (2016), suggesting SHS at home increased preterm birth (OR=1.16, 95% CI, 1.05-1.29) was utilised. Table 5.9 provides the estimated values.

Table 5.9: Probability of premature birth within pregnancy morbidities contingent on the severity of smoking and SHS

SHS	Conditions	Former smoker	Light smoker	Moderate smoker	Heavy smoker
YES	Placental abruption	0.4020	0.4143	0.4143	0.4316
	Placenta previa	0.2740	0.2842	0.2842	0.2989
	Pre-eclampsia	0.2642	0.2741	0.2741	0.2885
	No complication	0.0659	0.0692	0.0692	0.0739
NO	Placental abruption	0.3669	0.4143	0.4143	0.4316
	Placenta previa	0.2455	0.2842	0.2842	0.2989
	Pre-eclampsia	0.2363	0.2741	0.2741	0.2885
	No complication	0.0574	0.0692	0.0692	0.0739

5.2.1.2.8 Risk of maternal mortality during pregnancy

Risk of maternal mortality was estimated based on the ONS Mortality Statistics (2006-2015). The number of deaths by pregnancy complications and mortality risks per condition are listed below (Table 5.10). Since there was no study showing SDP or SHS during pregnancy was associated with maternal mortality, it was assumed that SDP or SHS did not have any impact on mortality during pregnancy.

Table 5.10: Number of deaths during pregnancy in ONS mortality statistics

Year	Number of deliveries	Death	Death from ectopic pregnancy	Death from miscarriage	Death from abruption	Death from previa	Deaths from pre-eclampsia	Other death
2014	685,341	46	3	1	1	0	1	40
2013	696,209	46	3	3	2	0	2	36
2012	722,254	46	0	0	1	0	4	41
2011	722,768	44	0	1	2	0	0	41
2010	722,357	35	1	0	0	0	2	32
2009	708,244	63	1	0	1	0	5	56
2008	706,376	44	3	2	0	0	3	36
2007	704,059	47	2	2	0	0	2	41
2006	682,303	41	2	0	1	1	4	33
Total	**6,349,911**	**412**	**15**	**9**	**8**	**1**	**23**	**356**

Since the number of women who suffered from a specific condition was not provided in the national mortality dataset, Jones (2015) estimated that by multiplying the risks for experiencing pregnancy-related conditions (ONS, 2018) by the number of women giving birth. The next step was to divide the number of deaths due to a specific condition by the number of women who experienced that condition. The same process was repeated, using more recent data to estimate the probabilities in the ESIP.H model (Table 5.11).

Table 5.11: Estimated number of conditions and mortality risks during pregnancy

Condition	Death	Occurrence	Risk of death
Ectopic pregnancy	15	96,056	0.00016
Miscarriage	9	371,520	0.00002
Placental abruption	8	25,282	0.00033
Placenta previa	1	41,468	0.00002
Pre-eclampsia	23	125,293	0.00019
No-complication	356	6,157,868	0.00006

5.2.1.2.9 Impacts of prematurity on infant birth weight and stillbirth

The probabilities for live birth and stillbirth by gestation length were estimated based on the most recent ONS Gestation-specific Infant Mortality in England and Wales and Child Mortality Statistics (ONS, 2019c, ONS, 2014b). These probabilities were different to those used by Jones et al. (2018) since they utilised the ONS data between 2006 and 2012 while in the current study the data between 2012 and 2014 was used. There was a change in the definition of stillbirth from 2012; hence data before that year was not included. The number of live births and stillbirth by birth weight and prematurity are provided in Table 5.12.

Table 5.12: Number of live births and stillbirth by birth weight and prematurity

	Premature low birth weight (LBW)		Premature normal birth weight (NBW)		Full gestation LBW		Full gestation NBW	
Year	**Live birth***	**Stillbirth†**	**Live birth***	**Stillbirth†**	**Live birth***	**Stillbirth†**	**Live birth***	**Stillbirth†**
2012**	31,174	2,149	19,189	222	18,805	201	651,212	974
2013	30,134	1,972	18,640	170	18,048	188	621,967	937
2014‡	29,598	2,000	19,955	185	18,079	182	614,650	873
Total	**90,906**	**6,121**	**57,784**	**577**	**54,932**	**571**	**188,7829**	**2,784**
Risk	**0.9369**	**0.0631**	**0.9901**	**0.0099**	**0.9897**	**0.0103**	**0.9985**	**0.0015**

*Source: Gestation-specific infant mortality in England and Wales (relevant year)
† Source: Table 9 Child Mortality Statistics (relevant year)
**Before 2012 the definition of stillbirth was defined as occurring before 36 weeks after 2012 the threshold changed to 37 weeks. Hence, data before 2012 was not included.
‡Latest gestation specific data was published in 2014.

Dietz et al. (2010) estimated odds ratios for LBW amongst full gestation infants by SDP groups (light, moderate, heavy respectively) as 2.3 (95% CI, 2.3-2.4), 3.1 (95% CI, 3.0-3.2) and 4.0 (95% CI 3.6-4.3) respectively. The corresponding figures for preterm infants were 1.4 (95% CI, 1.3-1.4), 1.5 (95% CI, 1.5-1.6), and 1.9 (95% CI, 1.7-2.1).

Regarding the impact of SHS, a systematic review by Salmasi et al. (2010) reported an increased risk (RR=1.16, 95% CI 0.99–1.36, 9 studies) compared to pregnant women who were not exposed to SHS. The probability of LBW according to the smoking status was calculated by applying the methods explained in Section 5.2.1.2.6 The estimated values are presented in Table 5.13.

Table 5.13: Probability of LBW conditional on smoking status and gestation

SHS Exposure	Conditions	Former smoker	Light smoker	Moderate smoker	Heavy smoker
YES	**Premature <37 weeks**	0.6363	0.6786	0.7070	0.7413
	Full gestation ≥37 weeks	0.0262	0.0315	0.0671	0.0850
NO	**Premature <37 weeks**	0.6013	0.6786	0.7070	0.7413
	Full gestation ≥37 weeks	0.0227	0.0315	0.0671	0.0850

A meta-analysis by Pineles et al. (2016) determined an increased stillbirth risk for each SDP group as follows; 1.12 (95% CI, 0.91-1.37) in former smokers, 1.10 (95% CI, 0.98-1.24, 20 studies) in light smokers, 1.30 (95% CI, 1.22-1.38, 9 studies) in moderate smokers, 1.24 (95% CI, 1.03-1.50, 10 studies) in heavy smokers. According to this data, heavy smokers had a lower increase in risk compared to moderate smokers, due to the inclusion of different studies for different SDP groups. Therefore, to ensure consistency

within the model, it was assumed that moderate and heavy smoking would have the same impact by applying the lowest ratio.

Additionally, Pineles et al. (2016) reported an increased risk related to SHS exposure during pregnancy (RR=1.37, 95 % CI, 1.04-1.82, 6 studies). However, since applying that risk ratio would result with assigning SHS-exposed former smokers higher risks than active smokers, the impact of SHS was assumed to be the same as light smoking by taking a conservative approach. The probability of stillbirth by different smoking exposure groups was calculated by using the methods described earlier (Section 5.2.1.2). The estimated probabilities are provided in Table 5.14.

Table 5.14: Probability of a stillbirth conditional on birth weight, gestation, and smoking status

SHS Exposure	Conditions	Former smoker	Light smoker	Moderate smoker	Heavy smoker
YES	**LBW/premature**	0.0660	0.0660	0.0744	0.0744
	NBW/premature	0.0103	0.0103	0.0116	0.0116
	LBW/ full gestation	0.0107	0.0107	0.0121	0.0121
	NBW/ full gestation	0.0015	0.0015	0.0017	0.0017
NO	**LBW/premature**	0.0672	0.0660	0.0744	0.0744
	NBW/premature	0.0105	0.0103	0.0116	0.0116
	LBW/ full gestation	0.0109	0.0107	0.0121	0.0121
	NBW/ full gestation	0.0016	0.0015	0.0017	0.0017

5.2.1.2.10 Health related quality of life parameters

Following the same approach as Jones et al. (2018), life years at the end of pregnancy were estimated based on the assumption that pregnancy would last 40 weeks and 10 weeks in case of ectopic pregnancy, 14 weeks for miscarriage, 33 weeks for premature birth, 38 weeks for previa and 39 weeks for pre-eclampsia in terms of quality of life. All women experiencing a foetal loss were assigned a 0.1 utility loss (Partridge et al.,

2012) and those suffering from ectopic pregnancy lost another 0.01 (Gillespe et al., 2012).

Unlike in the earlier version of ESIP, in this study the quality of life impacts were incorporated by SDP groups (light, moderate and heavy) based on the values calculated by Maheswaran et al (2013), which are provided in Table 5.15. However, no data was identified for the impact of SHS on health utilities, and thus, it was assumed that SHS had no impact on quality of life.

Table 5.15: Utility tariff for smokers and non-smokers

Risk factor	Utility decrement	95% Confidence Interval
Constant	0.987	0.974 – 1
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 2013

5.2.1.3 Costs attributable to pregnancy and associated complications

The list of the pregnancy associated conditions used to calculate the costs are provided in Appendix 9 along with the relevant HRG codes (2017-2018). Table 5.16 below shows the cost components used in ESIP.H, estimated based on the 2017-2018 NHS reference costs.

Table 5.16: Weighted mean costs for model outcomes

	Description	Weighted mean cost
Foetal loss	Treatment for ectopic pregnancy	£690.06
	Threatened or spontaneous miscarriage	£614.80
Antenatal care	Community midwife visit	£56.00
	Standard ultrasound scan	£113.00
	Specialised ultrasound scan	£133.00
	Obstetrician first visit	£164.00
	Obstetrician subsequent visit	£125.21
Antenatal drugs	Hypertension in pregnancy drug treatment cost	£9.98 per pack of 56 tablets*
Delivery	Birth	£3,134.91
	Caesarean	£4,461.68
	Emergency Caesarean	£5,036.69
Hospital care	Routine observation (per day)	£486.00
Death	Cardiac Arrest	£1,620.21

*Data taken from BNF 76 September 2018

5.2.1.3.1 Estimating maternal healthcare costs

The methodology applied by Jones (2015) was used to estimate the costs associated with pregnancy, using 2017-2018 NHS reference costs instead of 2011-2012. The following assumptions made by Jones (2015) after consulting a practicing NHS midwife were also used in ESIP.H:

- Ectopic pregnancy and miscarriage: hospital care costs, and one ultrasound scan.
- If pregnancy ends with delivery: the costs of eight community midwife visits and two ultrasound scans, a birth. Mothers who give birth before 37 weeks receive six midwife visits rather than eight visits received by those who have a full-term pregnancy.
- Placental abruption: the costs of an emergency caesarean birth, one obstetrician visit, and three days' routine observation in hospital. Mothers who give birth before 37 weeks receive six midwife visits rather than eight visits received by those who have a full-term pregnancy.

- Placenta previa: antenatal care and an additional ultra-sound scan, three obstetrician visits, birth by caesarean section with three days' routine observation. Mothers who give birth before 37 weeks they receive six midwife visits rather than eight visits received by those who have a full-term pregnancy.

- Preeclampsia: antenatal care and three obstetrician visits, three extra ultrasound scans, three days' routine observation, and medication for the mother's blood pressure. The standard care is to offer a 200mg tablet of twice a day. Based on the assumption that pre-eclampsia develops at week 20 of pregnancy, in the case of premature birth five packs would be required while in full gestation that six packs would be provided.

- Delivery cost: The cost of a caesarean section was applied for both abruption and previa. If it was a normal pregnancy, any mode of delivery could be required, and hence all costs were used to estimate an average cost.

- Death: All costs until death and the cost of death were applied.

5.2.1.3.2 Infant-related costs

The HRG codes used for estimating the infant-related costs are provided in Appendix 10. Regarding the cost of neonatal care, Jones et al. (2018) estimated a weighted cost (£15,934.55), given the costs would vary depending on the gestational age of the infant due to the length of stay in the neonatal intensive unit. A probabilistic estimation was conducted to obtain the costs of healthcare services provided for preterm and full gestation babies based on the average length of stay by birth weight (<27 weeks, 28-31 weeks, 32-36 weeks, 37 weeks), applying the following formula:

$$Cost\ of\ neonatal\ care\ for\ preterm\ birth\ infants\ =$$

$$(LS27\ \times\ PNC27) \times \left(\frac{P27}{TP}\right) + (LS28\ \times\ PNC28) \times \left(\frac{P28}{TP}\right) + (LS32\ \times\ PNC32) \times \left(\frac{P32}{TP}\right)$$

where LS27 is the length of stay for infants born earlier than 27 weeks, PNC27 is the probabilistic cost of neonatal care for the same group, P27 is the number of premature births in the group, and TP is the total premature births. Similarly, LS28 stands for the length of stay for infants born between the 28th and 31st weeks. The cost of neonatal care for full gestation babies was estimated by using the same formula. The same calculation was repeated for 10,000 times based on the distributions and the mean of those figures was the cost of neonatal care for premature infants. The excel sheet of this estimation was provided in the appendix (Appendix E currency codes with macro) of the article published by Jones et al. (2018). The same process was repeated for the ESIP.H model. Table 5.17 presents the estimated costs related to the infant model in ESIP.H.

Table 5.17: Costs related to infant healthcare

Condition	Costs
Stillbirth	£ 1,193.37
Neonatal care for preterm	£16,057.37
Neonatal care for full gestation	£2,704.08

5.2.2 Mother Lifetime Component

5.2.2.1 Model structure

A Markov model was used to estimate the lifetime health outcomes of smoking on women and the associated costs. ESIP distinguished women who stayed abstinent less than a year from those who were abstinent for a longer period by introducing three separate health states for former smokers. This was necessary because most former smokers relapse within the first year of a quit attempt. ESIP.H further improved that by

incorporating the impact of partners' smoking and the severity of smoking to the model.

ESIP.H uses annual cycles as in the ESIP model and 0-1 year quitter and 1-2 year quitter states were designed as tunnel states; women cannot remain more than a year in these states. Additionally, women could not transit from one smoker state to another, thus it was assumed for example that heavy smokers would remain heavy smokers, quit or die. However, those who quit can relapse to any of the three smoker statuses. The ESIP.H mother component includes 13 states; eight states more than the states in the ESIP model.

1. Light smoker (LS)
2. Moderate smoker (MS)
3. Heavy smoker (HS)
4. 0-1 year quitter (0-1Q)
5. 1-2 year quitter (1-2Q)
6. Long-term quitter (LTQ)
7. Light smoker exposed to SHS (LSSHS)
8. Moderate smoker exposed to SHS (MSSHS)
9. Heavy smoker exposed to SHS (HSSHS)
10. 0-1 year quitter exposed to SHS (0-1QSHS)
11. 1-2 year quitter exposed to SHS (1-2QSHS)
12. Long-term quitter exposed to SHS (LTQSHS)
13. Dead

The simplified structure of the mother lifetime component (MLC) is shown in Figure 5.5.

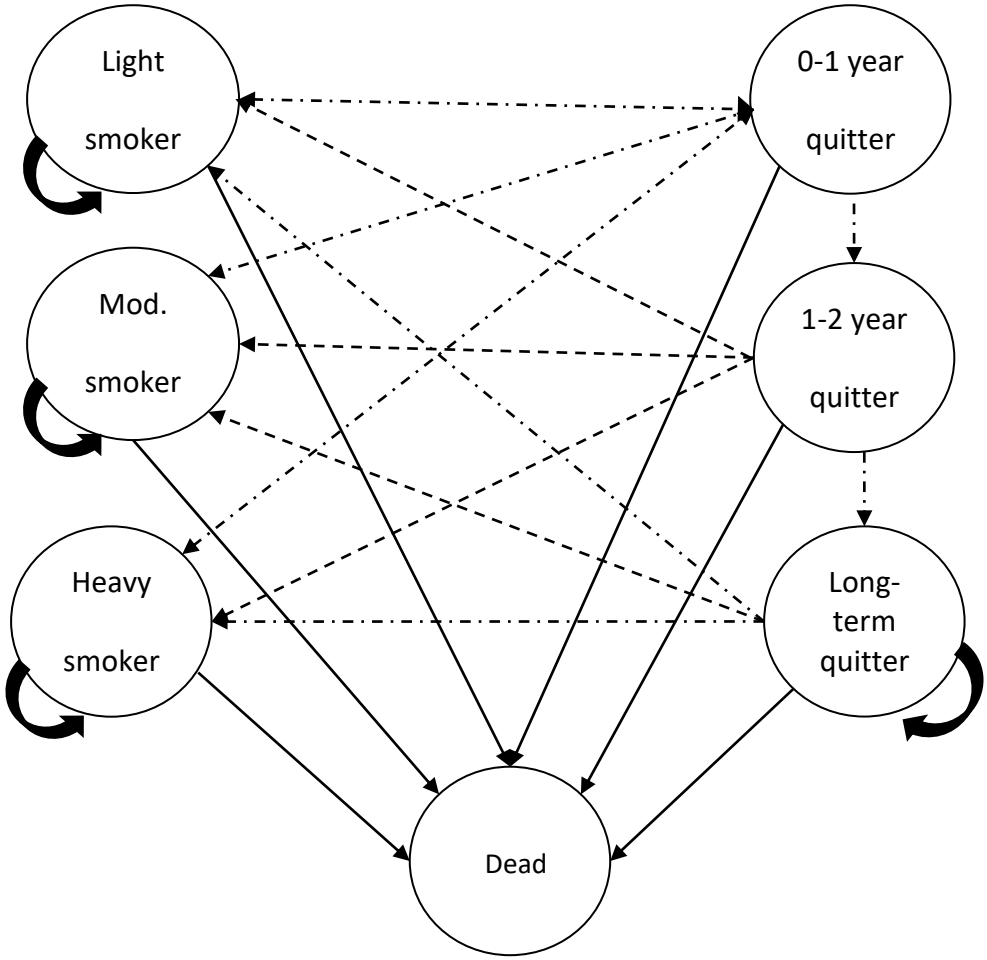


Figure 5.5: Simplified Markov model structure of the MLC

Although the model allows transition between SHS-exposed and unexposed health states those are not shown in Figure 5.5 for illustration simplicity, and thus it includes only half the health states. Figure 5.6 provides the transitions for light smokers as an example in more detail.

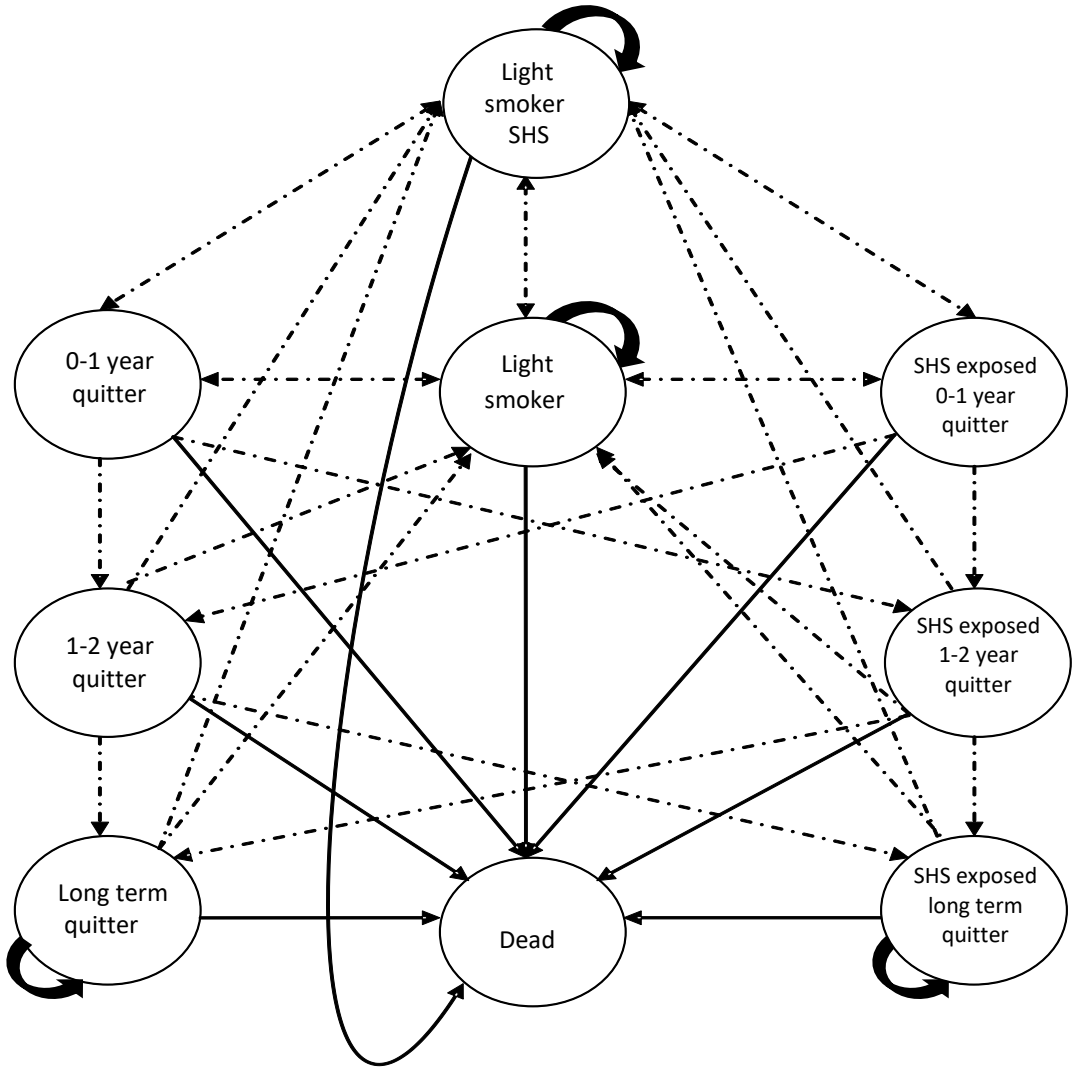


Figure 5.6: Markov structure for light smokers

Table 5.18 below shows how transition probabilities were calculated in ESIP.H, where P (MQ) stands for "mother's probability of quitting", MD for "mother dead", PNS for "partner not smoking", PCS for "partner current smoker", P(PNSIPNS) for "probability of non-smoking partner staying non-smoker". Additionally, 0.46, 0.40 and 0.41 are the proportions of light moderate and heavy smokers among female smokers in the general population (ONS, 2018a).

Table 5.18: Transition probabilities in the mother lifetime component

	Transiting to:												
	1. LS	**2. MS**	**3. HS**	**4. 01Q**	**5. 12Q**	**6. LTQ**	**7. LSSHS**	**8. MSSHS**	**9. HSSHS**	**10. 01QSHS**	**11. 12QSHS**	**12. LTQSHS**	**13. Dead**
1	(1- P(MQ)-P(MD))* P(PNSIPNS)	0	0	P(MQ) *P(PNSIPNS)	0	0	(1- P(MQ)-P(MD))* P(PCSIPNS)	0	0	P(MQ)* P(PCSIPNS)	0	0	P(MD)
2	0	(1- P(MQ)-P(MD))* P(PNSIPNS)	0	P(MQ) *P(PNSIPNS)	0	0	0	(1- P(MQ)-P(MD))* P(PCSIPNS)	0	P(MQ)* P(PCSIPNS)	0	0	P(MD)
3	0	0	(1- P(MQ)-P(MD))* P(PNSIPNS)	P(MQ) *P(PNSIPNS)	0	0	0	0	(1-P(MQ)-P(MD))* P(PCSIPNS)	P(MQ)* P(PCSIPNS)	0	0	P(MD)
4	Nrelapsers* 0.46 (A)* P(PNSIPNS)	Nrelapsers* 0.40 (B)* P(PNSIPNS)	Nrelapsers* 0.14 (C)* P(PNSIPNS)	0	1-A-B-C-P(MD)	0	(A)* P(PCSIPNS)	(B)* P(PCSIPNS)	(C)* P(PCSIPNS)	P(PCSIPNS)	0	0	P(MD)
5	(A)* P(PNSIPNS)	(B) *P(PNSIPNS)	(C)* P(PNSIPNS)	0	0	1-A-B-C-P(PCSIPNS)-P(MD)	(A)* P(PCSIPNS)	(B)* P(PCSIPNS)	(C)* P(PCSIPNS)	0	P(PCSIPNS)	0	P(MD)
6	(A)* P(PNSIPNS)	(B)* P(PNSIPNS)	(C)* P(PNSIPNS)	0	0	1-A-B-C-P(PCSIPNS)-P(MD)	(A)* P(PCSIPNS)	(B)* P(PCSIPNS)	(C)* P(PCSIPNS)	0	0	P(PCSIPNS)	P(MD)
7	(1-P(MQPCS)-P(MD))* P(PNSIPCS)	0	0	P(MQ)* P(PNSIPCS)	0	0	(1-P(MQ)-P(MD))* P(PCSIPCS)	0	0	P(MQ)* P(PCSIPCS)	0	0	P(MD)
8	0	(1-P(MQ)-P(MD))* P(PNSIPCS)	0	P(MQ)* P(PNSIPCS)	0	0	0	(1-P(MQ)-P(MD))* P(PCSIPCS)	0	P(MQ)* P(PCSIPCS)	0	0	P(MD)
9	0	0	(1-P(MQ)-P(MD))* P(PNSIPCS)	P(MQ)* P(PNSIPCS)	0	0	0		(1-P(MQ)-P(MD))* P(PCSIPCS)	P(MQ)* P(PCSIPCS)	0	0	P(MD)
10	(A)* P(PNSIPCS)	(B)* P(PNSIPCS)	(C)* P(PNSIPCS)	0	P(PNSIPCS)	0	(A)* (PCSIPCS)	(B)* (PCSIPCS)	(C)* (PCSIPCS)	0	1-A-B-C-P(MD)	0	P(MD)
11	(A)* P(PNSIPCS)	(B)* P(PNSIPCS)	(C)* P(PNSIPCS)	0	0	(1-A-B-C-P(MD))* P(PNSIPCS)	(A)* (PCSIPCS)	(B)* (PCSIPCS)	(C)* (PCSIPCS)	0	0	(1-A-B-C-P(MD))* P(PCSIPCS)	P(MD)
12	(A)* P(PNSIPCS)	(B)* P(PNSIPCS)	(C)* P(PNSIPCS)	0	0	(1-A-B-C-P(MD))* P(PNSIPCS)	(A)* (PCSIPCS)	(B)* (PCSIPCS)	(C)* (PCSIPCS)	0	0	(1-A-B-C-P(MD))* P(PCSIPCS)	P(MD)
13	0	0	0	0	0	0	0	0	0	0	0	0	1

5.2.2.2 Model parameters

5.2.2.2.1 Smoking behaviour during two years after delivery contingent on SHS exposure

Following the same approach adopted in the ESIP model, specific probabilities were used for the first two years after delivery. The IFS (HSCI, 2010a) data reported that by 10 months after delivery 13% of women who smoked throughout pregnancy quit. Additionally, 74% of those who quit smoking during pregnancy relapsed to smoking by six months after delivery according to the two trials included in the recent systematic review by Jones et al. (2016) that reported bio-chemically verified continuous abstinence (Hajek et al., 2001, Gielen et al., 1997).

There was no study reporting verified abstinence one year after delivery in the review by Jones et al. (2016). However, Ratner et al. (1999) reported that 20% of pregnant women who quit at delivery remained abstinent at one year based on CO verified measurement. Hence, 80% of women who quit smoking at delivery would relapse by one year after delivery.

The aforementioned formula by Flack et al. (2007) was applied to estimate the probability of abstinence and relapse 10 months after delivery for women who were not exposed to SHS. Where P stands for probability, RR for relative risk and Y for prevalence:

$$P(Quit_{SHSUNexposed\ \&\ SHSexposed}) = P(Quit_{SHSexposed}) \times \mathrm{Y_{SHSexposed}} + P(Quit_{SHSUNexposed}) \times \mathrm{Y_{SHSUNexposed}} \quad [1]$$

The probability of quitting among the SHS-exposed could be written as:

$$P(Quit_{SHSexposed}) = P(Quit_{SHSUNexposed}) \times \mathrm{RR_{SHSexposed}} \quad [2]$$

When the equation [2] was applied to equation [1]:

$$P(Quit_{SHSUNexposed}) = \frac{P(Quit_{SHSUNexposed\ \&\ SHSexposed})}{Prevalence_{SHSexposed} \times RR_{SHSexposed} + (1 - Prevalence_{SHSexposed}) \times 1}$$

Ratner et al. (1999) found that pregnant quitters who had smoking partners were more likely to be smoking one year after delivery (RR=1.81, 95% CI, 1.02-3.2). The proportion of pregnant women living with smoking partners one year after delivery was 0.41 in the study by Ratner et al. (1999). However, that figure was deemed too low, considering 0.68 of women smoking at delivery reported having a smoking partner during delivery (HSCI, 2010a). Additionally, in the study by Praddy et al. (2012) nine months after delivery 0.61 of women who quit at delivery had smoking partners. Applying the relative risk estimated by Ratner et al. (1999) and the probability of living with a smoking partner reported by Praddy et al. (2012), abstinence within the first year after delivery by SHS exposure was estimated at 0.03 in SHS exposed and 0.46 in SHS unexposed.

Since no study was identified that reported the impact of having a smoking partner on quit rates during the second year after delivery, wider evidence was sought. A longitudinal study of British smokers (Chandola et al., 2004) reported that in 10 years,

smokers who lived with other smokers were less likely to quit (aOR=0.65, 95% CI 0.40-1.05). However, this study identified quitters as those who stayed abstinent for at least two consecutive years within the study period of 10 years, and thus their findings were not appropriate for use in the ESIP.H model. According to a US-based study (Messer et al., 2008), smokers living in a smoke-free house were more likely to quit after a year (aOR=1.44, 95% CI 0.97-2.21). When the risks reported by Ratner et al. (1999) and Messer et al. (2008) were applied to the formula above, the postpartum quit and abstinence rates by SHS exposure were obtained.

The probability of becoming a long-term quitter (0.72) for those who stayed abstinent for more than one year (1-2Q) was taken from the systematic review conducted by Jones (2015) to identify quit and abstinence rates in smoking cessation interventions aimed at pregnant women. Because there was no data about the impact of SHS exposure on abstinence after the first year, wider evidence was sought.

Hyland et al. (2006) reported that among former smokers (n=2,341), those who lived in a smoke-free house were less likely to relapse four years later compared to individuals who lived in a household where smoking was allowed (RR= 0.60, 95% CI, 0.40-0.80). Although the impact of living with another smoker on relapse rates two years after quitting by the point of delivery might be higher than the relapse rates in the general population, in the absence of better evidence, it was deemed appropriate to apply those figures, taking a conservative approach.

The estimated transition probabilities based on SHS exposure for the initial two years are provided in Table 5.19.

Table 5.19: Smoking behaviour within two years after delivery contingent on SHS exposure

SHS exposure		Transition probabilities
YES	P(1-2 quit| 0-1 quit)	0.03
	P(Long-term quit| 1-2 quit)	0.66
	P(0-1 quit | CS)	0.11
NO	P(1-2 quit| 0-1 quit)	0.46
	P(Long-term quit| 1-2 quit)	0.80
	P(0-1 quit | CS)	0.16

5.2.2.2.2 Smoking behaviour within two years after delivery contingent on the severity of smoking and SHS

Some studies have reported that each additional cigarette consumed just before pregnancy increased the probability of relapse during the year following delivery among those who quit before pregnancy (Kia et al., 2018, Ratner et al., 1999), however none has reported on the impact of severity of SDP on quit attempts and relapse rates. Therefore, evidence from outside the postpartum period was sought.

Although some studies in the UK found that the severity of smoking was correlated with quit attempts they used a measure called the Heaviness of Smoking Index instead of cigarette consumption per day (Hyland et al., 2006, Borland et al., 2010, Borland et al., 2012) and none of those findings was reported in enough detail to be appropriate for the estimates for the current study.

The above mentioned study by Messer et al. (2008) found that moderate and heavy smokers were less likely to quit compared to light smokers and people living with other smokers were less likely to quit than those who did not live with other smokers. Table 5.20 presents the relative risks by the severity of smoking and SHS exposure.

Table 5.20: Relative risks for quitting based on the severity of smoking and SHS exposure

SHS-exposed	Light	Moderate (RR, 95% CI)	Heavy (RR, 95% CI)
YES	Reference	0.47 (0.30-0.76)	0.35 (0.23-0.53)
NO	Reference	0.57 (0.32-1.00)	0.43 (0.23-0.78)
Source: Author's estimations based on Messer et al. 2008			

To estimate the transition probabilities for quit attempts up to two years following delivery by the severity of smoking, the figures reported above (Table 5.20) were adjusted according to the following formula where P is the probability and Y the prevalence:

$$Probability\ (0-1\ \text{quit} \mid \text{CS}_{\text{SHSUNexposed}}) =$$

$$\frac{Probability\ (0-1\ \text{quit} \mid \text{CS})}{(1 \times Y_{SHSUNexposed}) + (P_{SHSexposed} \times Y_{SHSexposed})}$$

$$Probability\ (0-1\ \text{quit} \mid \text{CS}_{\text{SHSUNexposed}}) = (P_{LS} \times Y_{LS}) + (P_{MS} \times Y_{MS}) + (P_{HS} \times Y_{HS})$$

$$Probability\ (0-1\ \text{quit} \mid \text{CS}_{\text{SHSUNexposed}}) = (1 \times Y_{LS}) + (P_{MS} \times Y_{MS}) + (P_{HS} \times Y_{HS})$$

$$Probability\ (0-1\ \text{quit} \mid \text{MS}) = P_{LS} \times RR_{MS}$$

$$Probability\ (0-1\ \text{quit} \mid \text{HS}) = P_{LS} \times RR_{HS}$$

The same process was repeated for SHS-exposure. The probability of SHS exposure at delivery among women who smoked at conception was 0.61 (Prady et al., 2012). The proportion of light (0.4), moderate (0.32) and heavy smokers (0.28) were taken from the same study used for the calculations in the pregnancy component (Cooper et al., 2017). Table 5.21 presents the estimated probabilities.

Table 5.21: Quitting probabilities contingent on the severity of smoking and SHS during the first two years after delivery

SHS-exposed	Transition probability	Light	Moderate	Heavy
YES	P(0-1 quit | CS)	0.17	0.08	0.06
NO	P(0-1 quit | CS)	0.23	0.13	0.10

Due to the memoryless feature of Markov states, it was not possible to identify subjects by the severity of their former smoking once they quit. However, to deal with that, those who relapsed to smoking were distributed into light (0.46), moderate (0.40) and heavy smokers (0.14) based on the proportions in the general population (ONS, 2018b).

5.2.2.2.3 Smoking behaviour beyond two years after delivery

In ESIP, general quitting behaviour among current smokers was identified based on the figures in the statistics on smoking in England (HSCI, 2010b) to estimate the transition probabilities outside the first two years after delivery (Jones, 2015). This data was adopted unaltered for the ESIP.H model because no more recent data has been published. According to this data, 27% of all female smokers would make a quit attempt in a given year, 6% of quitters would remain abstinent for a year and 8% for more than two years.

Regarding relapsing after at least two years of abstinence, Jones (2015) used the results of a trial (Yudkin et al., 2003) to obtain the transition probability between long-term quitter and smoker states. The same probabilities were used in ESIP.H, which are reproduced in Table 5.22.

Table 5.22: Transition probabilities for general population outside two years postpartum

Transition probabilities	Percentage
Current smoker making any quit attempt in a given year P(0-1 quit | CS)	0.27[†]
Probability of remaining abstinent for a year but less than two P(1-2 quit| 0-1 quit)	0.14 (0.06[†] + 0.08[†])
Probability of remaining abstinent more than two P(Long-term quit| 1-2 quit)	0.57 (0.08[†] / 0.14)
Relapse to smoking in any year after at least two years abstinence	0.0086

[†] Source: Tables 3.6 and 3.7 in HSCI (2010b)

5.2.2.2.4 Smoking behaviour beyond two years after delivery contingent on the severity of smoking and SHS

The quitting probability outside pregnancy and the postpartum period (0.27) reported in Table 5.22 was adjusted based on the aforementioned relative risks related to the severity of smoking (Table 5.20) by Messer et al. (2008). A further adjustment was made to incorporate the impact of SHS on abstinence, according to the findings of Hyland et al. (2006). The proportion of light, moderate and heavy smokers in female smokers in the general population was 0.46, 0.40, and 0.14 (ONS, 2018b). There was no national data on the probability of living with another smoker for smoking individuals, hence an average of the proportions reported in two trials (0.33) was used for the calculations (Hyland et al., 2006, Messer et al., 2008). Additionally, as stated above, those who relapsed to smoking were allocated to light, moderate and heavy smoker states. The estimated transition probabilities are provided in Table 5.23.

Table 5.23: Transition probabilities outside delivery contingent on the severity of smoking and SHS

SHS	Transition probability	Light	Moderate	Heavy	Overall
YES	P(0-1 quit | CS)	0.30	0.14	0.11	-
	P(1-2 quit | 0-1 quit)	-	-	-	0.11
	P(LTQ| 1-2 quit)	-	-	-	0.49
	P(CS | LTQ)	-	-	-	0.011
NO	P(0-1 quit | CS)	0.40	0.23	0.17	-
	P(1-2 quit| 0-1 quit)	-	-	-	0.17
	P(LTQ| 1-2 quit)	-	-	-	0.62
	P(CS | LTQ)	-	-	-	0.007

5.2.2.2.5 SHS by partner after delivery

Since SHS exposure of women might change over time this was reflected in the model too. This means women were able to transit between SHS-exposed and SHS-unexposed health states. Since there is no data on how SHS exposure changes over time, SHS exposure was solely based on the partner's smoking behaviour. It was assumed that all smoking partners would expose women to SHS. Additionally, women who did not have partners were grouped with those having non-smoking partners since both groups of women are SHS-unexposed.

5.2.2.2.6 Mortality prevalence contingent on smoking

ESIP used the ONS mortality rate estimations and projections as the baseline risks (ONS, 2013). That was updated to the most current data in ESIP.H (ONS, 2019f). Since there is evidence showing a positive association between the number of cigarettes consumed and mortality rates, the impact of the severity of smoking on mortality was incorporated in the ESIP.H model, whereas this was not included in the ESIP model (Doll et al., 2004).

The probability of death for never smokers was estimated by applying the same formula used in the previous estimations where Y stands for prevalence (Flack et al., 2007):

$$\text{Prevalence}(\text{Mortality}|\text{NS}) = \frac{\text{Y}(\text{Mortality}|\text{Population})}{\text{Y}_{\text{NS}} + \left(\text{Y}_{\text{CS}} \times \text{RR}_{\text{CS}}\right) + \left(\text{Y}_{\text{FS}} \times \text{RR}_{\text{FS}}\right)}$$

To apply the above formula on the ONS mortality data, identifying the relative risk of death for former and current smokers was required. Doll and colleagues (1994) calculated all-cause mortality rates for current and former smokers compared to never smokers by age but not by the severity of smoking. In their later study (Doll et al., 2004) with the same cohort, death rates were estimated for light, moderate and heavy smokers but not jointly by age groups. Hence, their estimations were adjusted, using the proportions (0.46, 0.40, and 0.14 in females; 0.40, 0.38, and 0.22 in males) from the Health Survey for England (ONS, 2018b). The relative risks for former smokers were taken from the former study (Doll et al. 1994) because the latter did not report them by age. The relative risk of death based on the severity of smoking is provided in Table 5.24.

Table 5.24: Relative risk of death among by age, contingent on smoking status

Females & males			Females			Males		
Age	**Former⁺**	**Current***	**Light***	**Moderate***	**Heavy***	**Light***	**Moderate***	**Heavy***
0-34	1	1	1	1	1	1	1	1
35-44	1.25	1.69	1.47	1.74	2.27	1.42	1.68	2.19
45-54	1.23	2.24	1.94	2.31	3.00	1.88	2.23	2.90
55-64	1.41	2.55	2.21	2.63	3.42	2.14	2.54	3.31
65-74	1.33	2.73	2.37	2.81	3.66	2.29	2.71	3.54
75-84	1.19	2.17	1.89	2.24	2.91	1.82	2.16	2.82
85+	1.07	2.17	1.89	2.24	2.91	1.82	2.16	2.82

⁺Source Doll et al. (1994), *Source Doll et al. (2004)

Jones (2015) assumed the risk of death would be the same as never smokers for people aged between 0 and 34 because Doll et al. (1994) did not report any estimation for that group; the same approach was followed for ESIP.H since no new evidence was identified. The prevalence of smoking by age was obtained from the latest Adult Smoking Habits in England (ONS, 2018a) data, which are shown in Table 5.25.

Table 5.25: Prevalence of smoking by age

	Females			Males		
Age	**Current smoker (%)**	**Former smoker (%)**	**Never smoker (%)**	**Current smoker (%)**	**Former smoker (%)**	**Never smoker (%)**
16-24	20	7	73	28	3	69
25-34	23	17	61	18	15	67
35-49	16	23	61	20	31	50
50-59	16	27	57	15	38	48
60+	10	33	57	9	45	46

Source: Tables 1 and 2, Adult Smoking Habits, England, ONS 2018

Following the same approach by Jones (2015), only women in the 1-2 year quitter (1-2Q) and long-term quitter (LTQ) states were assigned the mortality rates for former smokers while women who were in the 0-1 year quitter (0-1Q) state were assigned the risks for current smokers. It was not possible to use the mortality rates for the previous health states (LS, MS, and HS) of women in their first year of abstinence since the transition probability from 01Q to current smoking was estimated based on the mortality rates as follows:

$$P(\ CS|0-1\mathrm{Q}) = 1 - \mathrm{P}(\mathrm{Dead}|0-1\mathrm{Q}) - \mathrm{P}(1-2\mathrm{Q}|0-1\mathrm{Q})$$

Additionally, applying the relative risks for current smokers to those who were abstinent for less than a year (0-1Q) would result with assigning a greater mortality risk to light smokers who just quit. Hence, it was appropriate to assume that individuals in the 0-1Q state would have the same mortality risk as light smokers.

5.2.2.2.7 Mortality prevalence contingent on second-hand smoke exposure

Hill et al. (2006) estimated the relative risk of death among non-smokers exposed to SHS as 1.28 (95% CI 1.16-1.42) in females and 1.16 (95% CI 1.04-1.30) in males aged 45 to 77. However, there was no evidence on the impact of SHS on mortality in former smokers. Thus, it was assumed that SHS did not increase the mortality risks among former smokers.

5.2.2.2.8 Morbidity prevalence in general population

In keeping with the ESIP model, ESIP.H included CHD, Stroke, LC and COPD in the mother lifetime component. ESIP.H used more up-to-date baseline risks for CHD, stroke and LC risks while the risks for COPD remained unchanged since no more recent data was available. To show the difference between the population risks, the figures for females used in ESIP compared to ESIP.H for the conditions are presented in Table 5.26 and the figures for COPD are provided in Appendix 12.

Table 5.26: Female morbidity prevalence in general population, comparing ESIP and ESIP.H

	CHD (%) ESIP	CHD (%) ESIP.H	Stroke (%) ESIP	Stroke (%) ESIP.H	LC (%) ESIP	LC (%) ESIP.H
0-15	0	0	0	0	0	0.0004
16-24	0.1	0.1	0.2	0.2	0	0.003
25-34	0.1	0.4	0.1	0.4	0	0.013
35-44	0.3	0.9	0.4	0.1	0	0.013
45-54	1.3	1.6	0.9	1.3	0.07	0.014
55-64	3.5	4.1	2.3	2.4	0.07	0.014
65-74	10	7.5	4.2	4.4	0.023	0.035
75+	19	17	11	9.4	0.023	0.041
Data year	2006	2011	2006	2011	1992	2015
Source	CHD Statistics Townsend, 2012Compendium of CHD Statistics 2012	HSE Adult Health Trends 2016	CHD statistics Townsend, 2012	HSE Adult Health Trends 2016	Forman et al. 2003	PHE 2016

ESIP.H also updated the prevalence of smoking by age to the most recent national data (ONS, 2018a), as shown in Table 26.7 Following the same methods described in section 5.2.1.2.6, the risks among never smokers were estimated as shown in Appendix 11.

Table 5.27: Proportion of current, former and never smokers in England

Age	Former smoker (%)	Current smoker (%)	Never smoker (%)
16-19	7	20	73
20-24	7	20	73
25-34	17	23	61
35-49	23	16	61
50-59	27	16	57
60+	33	10	57
Source: Adult smoking habits, 2018			

5.2.2.2.9 Morbidity risk contingent on the severity of smoking

There was strong evidence indicating a gradient between the number of cigarettes consumed and the morbidity risks. The relative risks for smoking-related morbidities for different smoking groups reported by discrete meta-analyses are provided in Table 5.288.

Table 5.28: Relative morbidity risks by the severity of smoking

		CHD (RR, 95% CI) (Hackshaw 2018)	COPD (RR, 95% CI) (Forey 2011)	Stroke (RR, 95% CI) (Hackshaw 2018)	LC (RR, 95% CI) (Keeffe 2018)
Female	Light	1.57 (1.29-1.91)	2.89 (2.41-3.45)	1.31 (1.13-1.52)	5.30 (3.52 -7.97)
	Mod.	1.76 (1.46-2.13)	6.21(4.72-8.16)	1.44 (1.22-1.70)	10.67 (7.43-15.33)
	Heavy	2.84 (2.21-3.64)	9.5 (7.38-12.22)	2.16 (1.69-2.75)	17.09 (12.11-24.11)
Male	Light	1.48 (1.30-1.69)	2.89 (2.41-3.45)	1.25 (1.13-1.38)	4.97 (2.74-9.03)
	Mod.	1.58 (1.39-1.80)	6.21 (4.72-8.16)	1.30 (1.18-1.43)	8.93 (4.90 -16.28)
	Heavy	2.04 (1.86-2.24)	9.5 (7.38-12.22)	1.64 (1.48-1.82)	14.61 (8.33-15.59)

For former smokers, the risk ratios reported in the Surgeon General's Report (CDC, 2014) were used because none of the systematic reviews calculated the ratios by age amongst former smokers.

Forey et al. (2011) and Keeffe et al. (2018) reported age-adjusted relative risk estimations for each smoking group (LS, MS and HS). Therefore, the age specific relative risks reported in the Surgeon General's Report, which was used in the ESIP model, were adjusted by applying the formula provided below according to the smoking severity specific estimations from those studies. Hacksaw et al. (2018) provided the relative risks for CHD and stroke by age and the severity of smoking but

the cohort study in the Surgeon General's report had a considerably bigger sample, indicating that their estimations would be more accurate. Additionally, Hackshaw et al. (2018) did not estimate the impact on former smokers and people on people aged 35 to 44. Hence the same adjustment was also applied to the age-adjusted figures reported by Hackshaw et al. (2018).

The adjustment was undertaken based on the proportion of light, moderate and heavy smokers in the original trials (Thun et al., 2013) which the Surgeon General's estimations were based on. In one of the trials from which the estimations for the 35-54 age group were obtained, the proportions were 0.16, 0.25 and 0.59 amongst females and 0.11, 0.17 and 0.77 in males. In the other trial, the proportions were 0.43, 0.36 and 0.19 amongst females 0.24, 0.36 and 0.39 in males. The estimated relative risks are provided in Appendix 12.

$$Relative\ risk\ for\ light\ smokers\ in\ a\ specific\ age\ group =$$

$$\frac{RR(Age\ group)}{RR\ (LS) \times Prevalence(LS) + RR\ (MS) \times Prevalence(MS) + RR\ (LS) \times Prevalence(LS)} \times RR(LS)$$

For example, the relative risk of having stroke for women aged 55 who were moderate smokers were estimated as follows. The Surgeon General's report estimated the relative risk of stroke for females aged 55 as 2.5 and the risks based on the severity of smoking by Hackshaw (2018) are reported above (Table 5.28).

$$\frac{2.5}{1.31 \times 0.43 + 1.44 \times 0.36 + 2.16 \times 0.19} \times 1.44 = 2.42$$

Similar to the mortality risk estimations, morbidity risks amongst former smokers were only applied to women in the 1-2Q and LTQ states. Morbidity estimations for those in the 0-1Q state were conducted based on their previous states (LS, MS, and HS).

5.2.2.2.10 Morbidity prevalence contingent on second-hand smoke exposure

To identify the impact of SHS on former smokers, meta-analyses that assessed SHS exposure by partner was sought. There was no systematic review investigating the impact of SHS on former smokers. However, two cohort studies (Malek et al., 2015, Vineis et al., 2005) reported that former smokers were more susceptible to the impacts of SHS, as shown in Table 5.299.

Table 5.29: Impact of SHS on former and never smokers in cohort studies

(HR, 95% CI)	Never smokers	Former smokers	Source
Stroke	1.17(0.80-1.72)	1.37 (0.97-1.95)	Malek (2015)
LC	1.05 (0.60-1.82)	2.32 (0.94-5.71)	Vineis (2005)
COPD	1.02 (0.63-1.66)	2.32 (1.07-5.01)	Vineis (2005)

Based on that evidence it was appropriate to apply the risk ratios for SHS on the probabilities for former smokers not on the probabilities for never smokers. Hence, the risk ratios reported by the most recent meta-analyses were applied; they are provided in Table 5.30.

Table 5.30: Relative risks for SHS-caused morbidity

(RR, 95% CI)	CHD (He et al., 1999)	COPD (Lee et al., 2018)	Stroke (Oono et al., 2011)	LC (Lee et al., 2016)
Female	1.24 (1.15-1.34)	1.26 (1.02-1.55)	1.25 (1.12-1.38)	1.22 (1.14-1.31)
Male	1.22 (1.10-1.35)	1.26 (1.02-1.55)	1.25 (1.12-1.38)	1.14 (1.01-1.29)

As in the pregnancy component of the model, the relative risks for SHS were applied on the probabilities for only SHS exposed former smokers and it was assumed that SHS had no additional impact on active smokers.

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

A worked example of how the stroke prevalence among moderate smokers aged 55 was calculated is provided below. The stroke prevalence was 2.4% (Table 5.26) and the proportion of former and active smokers was 27% and 16% respectively (Table 5.27) among 55 year old women. The relative risk was 2.5 for female smokers and 1.10 for former smokers (Section 5.2.2.2.9).

$$\frac{2.4\%}{27\% \times 1.10 + 16\% \times 2.5 + 57\%} = 0.019$$

The proportion of non-smoking women exposed to SHS is 24% (HSE, 2017) and the relative risk for SHS-exposed non-smokers is 1.25 (Table 5.30). The stroke risk among non-smoking women who were not exposed to SHS was estimated as follows:

$$\frac{0.019}{24\% \times 1.25 + (1 - 24\%)} = 0.0178$$

The relative risk for moderate smokers who are 55 years old was 2.42.

$$2.42 \times 0.0178 = 0.043$$

This shows that the prevalence of stroke among 55 years old women is approximately 4%. Similarly, the risk for non-smoking females exposed to SHS aged 55 would be 2%.

$$1.25 \times 0.0178 = 0.022$$

The estimated probabilities for lifetime morbidities amongst never smokers are provided in Appendix 12.

5.2.2.2.12 Adjustment for competing health risks in the lifetime components

Similar to the assumptions made in the ESIP model, ESIP.H assumed the probability of experiencing different health conditions was independent from each other. The total number with morbidities was estimated with the following formula in ESIP:

$$P(Morbidity) = P(CHD) + P(COPD) + P(LC) + P(Stroke)$$

This additive formula is only correct if the morbidities are mutually exclusive. That is also a good approximation of the following if the probabilities are low enough (Hoogenveen et al., 2017):

$$P(Morbidity) = 1 - (1 - P(CHD)) \times (1 - P(COPD)) \times (1 - P(LC)) \times (1 - P(Stroke))$$

However, the former becomes problematic if the total gets a value higher than 100%. To overcome that issue, the second formula was used in ESIP.H.

5.2.2.2.13 Health related quality of life in the MLC

For individuals who developed morbidities, related reductions in utilities were applied. The reductions in health utilities applied by Jones (2015) were also used in the ESIP.H model. Those values are reproduced in Table 5.311. The health utilities associated with smoking were assigned as in the pregnancy component and future utilities were discounted at a rate of 3.5% annually.

Table 5.31: QALY weights related with smoking caused morbidities

Condition	Mean utility score	Standard deviation	Source
CHD	0.73	0.30	MEDMAN study (2007)
COPD	0.73	0.23	Starkie et al (2011)
LC	0.67	0.22	Pickard et al (2007)
Stroke	0.72	0.32	Haacke et al (2006)
Source: Jones, 2015:230			

5.2.2.2.14 SHS and health related quality of life

Some studies showed significant impact of SHS on never smokers' health related quality of life in different settings (Bridevaux et al., 2007, Chen et al., 2015, Kang, 2015, Kristina et al., 2018). However, there was no analysis from a UK perspective. Therefore, it was assumed that SHS had no impact on QALY values.

5.2.2.2.15 Smoking related morbidity costs in the MLC

As in the previous version of ESIP, an NHS and Personal Social Services (PSS) perspective was adopted for costs. The costs used by Jones et al. (2018), identified from the literature, were used in ESIP.H after the inflation to 2017-2018 prices, since there was no more recent estimation of the costs accrued from CHD, COPD, lung cancer and stroke in the UK. Those values are shown in Table 5.32Table 5.32. The cost of death identified for the WPC of the model was used in the MLC too. Following NICE recommendations, costs were discounted at a rate of 3.5% annually (NICE, 2013a).

Table 5.32: Smoking related lifetime morbidity costs per patient

	Cost	Standard Error	Source
CHD	£1,943.74	Not available	Liu et al. (2002)
COPD	£8921.88	Not available	European Respiratory Society (2014)
LC	£10,101.27	Not available	European Respiratory Society (2014)
Stroke	£22,966.96 (five years)	£147.96	Youman et al. (2003)

5.2.3 Partner Lifetime Component

5.2.3.1 Model structure

Partner lifetime component (PLC) was modelled in a separate Markov chain. This included the same states as for women (LS, MS, HS, 0-1Q, 1-2Q, LTQ, LSSHS, MSSHS, HSSHS, 0-1QSHS, 1-2QSHS, LTQSHS, dead) and two additional states for never smokers (NS, NSSHS) as shown in Figure 5.7. Although the model allows transition between SHS-exposed and unexposed health states those are not shown in Figure 5.7 for illustration simplicity. Hence, only half the transitions for light smokers are displayed below.

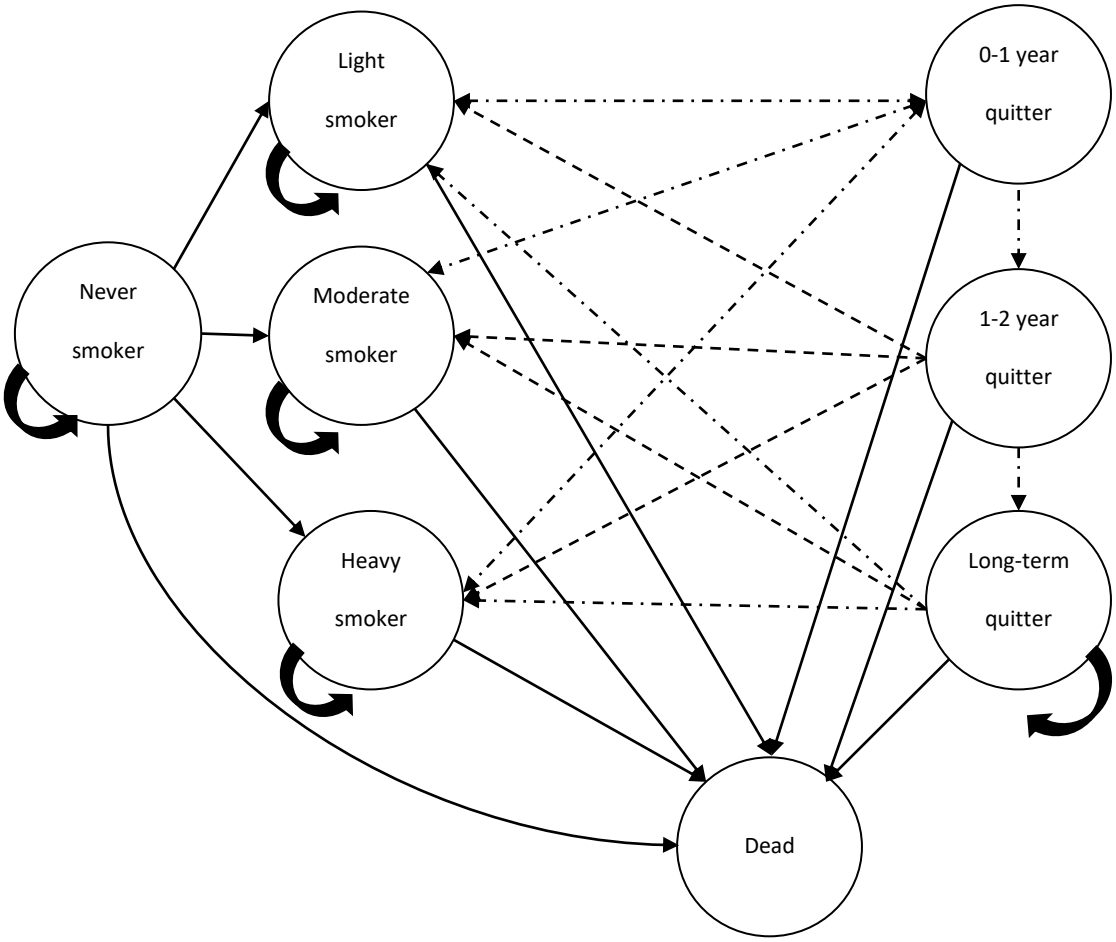


Figure 5.7: Simplified Markov model structure of the partner lifetime component

5.2.3.2 Probability parameters

5.2.3.2.1 Partner smoking behaviour

The model uses the SHS probability in the within pregnancy component (0.65) as the proportion of smoking partners at delivery unless the user enters different values. Similarly, the proportion of partners who quit is estimated based on the figure (0.05) reported by Ratner et al. (1999). Hence, 0.03 of partners would be those who smoked at conception and quit at delivery while the remaining 0.32 are never smokers.

The proportion of light (0.40), moderate (0.38) and heavy smokers (0.22) among smoking males were taken from the Health Survey for England (ONS, 2018b). According to the Infant Feeding Survey (IFS) (HSCI, 2010a) data, of partners who has smoked during pregnancy, 72% continued to smoke while 28% quit by 10 months after delivery. However, that rate was higher than the rates for mothers which were identified based on trial data. Hence, recent trial data was sought.

There was no study reporting biologically confirmed relapse rates among partners who quit smoking at delivery. Hence the relapse rates for mothers (0.03 and 0.46) were applied in PLC as well. Additionally, McBride et al. (2004) reported that 3% of partners who smoked during pregnancy were quit by one year after delivery. That figure was adjusted according to the findings of the study by Messer et al. (2008) and 98% SHS rate, considering among pregnant smokers 2% would be abstinent at one year after delivery (1-0.09*0.2). For this adjustment the same formula explained in Section 5.2.2.2 was used (Flack et al., 2007). Thus, quitting probability within the first year after delivery was 0.06, 0.03 and 0.03 for partners (LS, MS and HS, respectively) who did not have a smoking partner and 0.05, 0.02 and 0.02 for those with a smoking partner.

Regarding the quit rates among males beyond two years after delivery, Jones et al. (2018) used the national figure of 0.25 (HSCI, 2010b) as the probability of quitting in a given year. Similar to mothers, partners had higher chance of quitting if they did not live with smoking individuals and smoked fewer cigarettes. The estimated probabilities were 0.39 (LS), 0.22 (MS), and 0.17 (HS) among partners not living with a smoker and

0.29 (LS), 0.14 (MS), and 0.10 (HS) in those living with a smoker. Similarly, the abstinence and relapse probabilities were the same as those used for mothers (Section 5.2.2.2.4).

In addition, partners who were never smokers at the point of delivery had the risk of starting smoking in any year. That was estimated based on the approach used in ESIP to calculate smoking uptake of children. To estimate the smoking uptake risk by age groups, Jones (2015) applied the following:

- the age at which fewest people reported having never smoked was identified for males and females (A)
- these values were subtracted from one to obtain the proportion of current smokers and former smokers (ever smokers) (B)
- the proportion of ever smokers was adjusted according to the starting age (C)

The same approach was followed in ESIP.H, updating the figures for never smokers (ONS, 2018a). The proportion started smoking at that age group was taken from the Statistics on smoking in England (ONS, 2014c) since no recent data has been published.

For example, 46% of males were never smokers at the age of 60 (A), which means 54% were ever smokers (B). Since proportion of current smokers who started smoking between the ages 25 and 50 was identified as 0.04, the proportion of 'ever smokers' who started smoking at that age group was estimated at 0.022 (0.54X0.04). Next, that was divided by the proportion of never smokers in that age group (0.022/0.55=0.046). That proportion was converted to an annual transition probability by applying the standard formula (Fleurence and Hollenbeak, 2007):

$$1 - e^{-0.046} = 0.045$$

Since there was no evidence showing the impact of living with smokers on smoking uptake among adults, it was assumed not to have any effect.

Probabilities of moving between SHS-exposed and unexposed states for women were estimated based on partners' quit and relapsing probabilities by applying the following formula:

$$P(\text{SHSunexposed}|\text{SHSexposed}) =$$

$$\frac{\left(P(01Q_ILS)+P(Dead_ILS)\right) X\ N_{LS}+\left(P(Dead_IMS)+P(01Q_IMS)\right) X\ N_{MS}+\left(P(Dead_IHS)+P(01Q_IHS)\right) X\ N_{HS}}{N_{LS}+N_{MS}+N_{HS}}$$

$$P(\text{SHSexposed}|\text{SHSunexposed}) =$$

$$\frac{P(CSI01Q)X\ N01Q + P(CSI12Q)X\ N12Q + P(CSILTQ)X\ NLTQ + P(CSINS)}{N01Q + N12Q + NLTQ + NNS + NDead}$$

5.2.3.2.2 Mortality, morbidity, and health related quality of life in the PLC

The probabilities for mortality, morbidity, and health related quality of life in PLC were obtained by using the same methods explained in Section 5.2.2 for MLC. The related figures are provided in Appendix 12.

5.2.4 Offspring Childhood Component

5.2.4.1 Model structure

This component (referred to as infant childhood component in ESIP) covered the impact of SHS during childhood as well as in utero smoke exposure. ESIP.H

incorporated partners' smoking as well as mothers', thus improving ESIP, by having a household perspective rather than focussing only on mothers.

ESIP first grouped children based on their exposure status during pregnancy and they entered the OCC model based on the smoking status of their mothers during pregnancy. The same approach was followed in ESIP.H, by taking into account both parents' smoking. In accordance with the increased number of health states in the MLC compared to ESIP, there were more childhood states in this version of the model as follows:

1. SHS unexposed mother quits smoking during pregnancy
2. SHS unexposed mother light smoker during pregnancy
3. SHS unexposed mother moderate smoker during pregnancy
4. SHS unexposed mother heavy smoker during pregnancy
5. SHS exposed mother quits smoking during pregnancy
6. SHS exposed mother light smoker during pregnancy
7. SHS exposed mother moderate smoker during pregnancy
8. SHS exposed mother heavy smoker during pregnancy

For each group, a separate Markov chain was produced. Those chains then were combined together to estimate the health and cost impact. ESIP separated children with smoking mothers in two groups based on their SHS exposure since not all smoking mothers expose their children to SHS. The same approach was followed in ESIP.H.

As in ESIP, the childhood model ends at the age of 15 and children move to the adulthood component at 16 in ESIP.H. This is because the smoking prevalence data in the UK is reported from the age of 16 and there is evidence that smoking uptake at this age is affected by the smoking status of parents (Leonardi-Bee et al., 2011, ONS,

2018a). Thus, producing a separate Markov chain after this age was appropriate. Every Markov chain in the offspring component included 25 health states as follows:

1. Offspring exposed to SHS/ Mother smokes (LS) father does not smoke
2. Offspring exposed to SHS/ Mother smokes (MS) father does not smoke
3. Offspring exposed to SHS/ Mother smokes (HS) father does not smoke
4. Offspring exposed to SHS/ Mother smokes (LS) father smokes
5. Offspring exposed to SHS/ Mother smokes (MS) father smokes
6. Offspring exposed to SHS/ Mother smokes (HS) father smokes
7. Offspring exposed to SHS/Father smokes mother 01Q
8. Offspring exposed to SHS/Father smokes mother 12Q
9. Offspring exposed to SHS/Father smokes mother LTQ
10. Offspring exposed to SHS/Mother dead father smokes
11. Offspring not exposed to SHS/ Mother smokes (LS) father does not smoke
12. Offspring not exposed to SHS/ Mother smokes (MS) father does not smoke
13. Offspring not exposed to SHS/ Mother smokes (HS) father does not smoke
14. Offspring not exposed to SHS/ Mother smokes (LS) father smokes
15. Offspring not exposed to SHS/ Mother smokes (MS) father smokes
16. Offspring not exposed to SHS/ Mother smokes (HS) father smokes
17. Offspring not exposed to SHS/Father smokes mother 01Q
18. Offspring not exposed to SHS/Father smokes mother 12Q
19. Offspring not exposed to SHS/Father smokes mother LTQ
20. Offspring not exposed to SHS/Mother dead father smokes
21. Offspring not exposed to SHS/ Father does not smoke mother 01Q
22. Offspring not exposed to SHS/ Father does not smoke mother 12Q
23. Offspring not exposed to SHS/ Father does not smoke mother LTQ
24. Offspring not exposed to SHS/Mother dead father not smoker
25. Offspring dead

As in the ESIP model, ESIP.H assumed that parents did not change their smoking behaviour around the child unless their smoking status changed. An illustration of the Markov model structure is provided below in Figure 5.8.

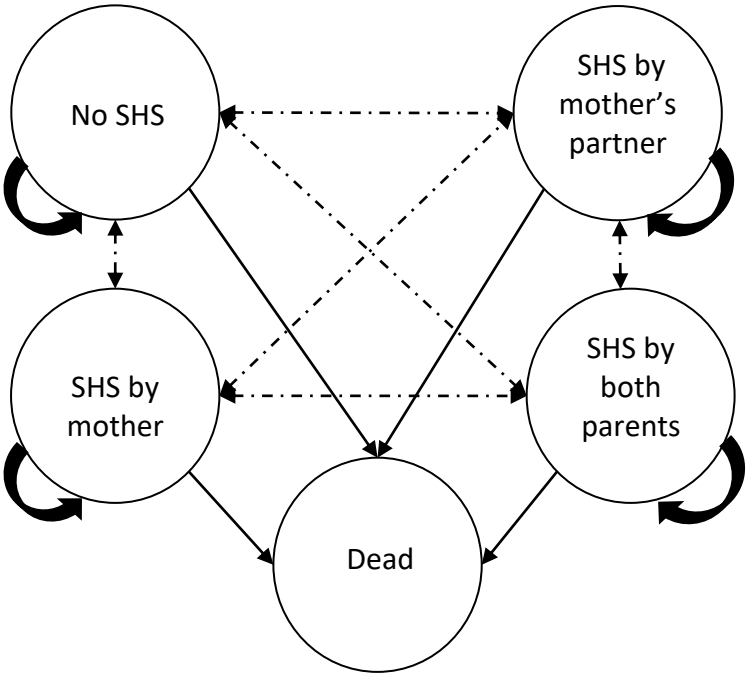


Figure 5.8: Simplified Markov model structure for OCC

5.2.4.2 Gender in the OCC

ESIP separated the OCC by gender due to the different mortality and morbidity burden for females and males (Jones 2015), using 51% as the proportion of males (ONS, 2014a). That remained unchanged in this version of the model.

5.2.4.3 SHS exposure in the OCC

ESIP used the figure reported by the smoking related behaviour and attitudes survey (ONS, 2013) to estimate the number of children exposed to SHS, which suggested only 23% of smoking individuals would smoke in the presence of children. The rate was 34% for heavy smokers and 20% for light and moderate smokers. However, Health Survey

for England (2017) found detectable cotinine levels among 80% of the children who had either or both parents smoking. Since biochemically verified results would be more reliable, ESIP.H used the latter figure (80%). Also, there is evidence showing children of heavy smokers are more likely to be exposed to SHS at home (Orton et al., 2014, Bakoula et al., 1997, Mantziou et al., 2009). Hence, that figure was adjusted according to the findings of the previous survey because the latter did not investigate the impact of the number of cigarettes consumed. Thus, in ESIP.H, 65% for children with light or moderate smoker mothers and 93% for those with heavy smoking mothers were exposed to SHS.

The proportion exposed to SHS amongst those who have light and moderate smoking mothers (65%) was also used if children were exposed to SHS by mother's partner only. When both parents smoked, the risk was calculated based on mother's probability of exposing their children to SHS since studies showed that the greatest part of SHS exposure was caused by maternal smoking (Orton et al., 2014, Delpisheh et al., 2006, Sims et al., 2010).

5.2.4.4 Cycle length

The childhood component utilised yearly cycles in accordance with the mother component. ESIP assumed that the children would be dependent on their mother during the first 15 years and modelled those years as the childhood component. That remained unchanged in ESIP.H.

5.2.4.5 Model parameters

5.2.4.5.1 Offspring mortality risk

ESIP.H used the updated mortality rate estimates and projections for the offspring mortality (ONS, 2018d). ESIP applied the odds ratios reported by Li et al. (2003), shown in Table 5.33, to adjust the mortality rate based on birth weight. The same figures were used in ESIP.H since no new evidence became apparent. SDP or SHS were assumed to have no impact on children's mortality risks due to lack of evidence.

Table 5.33: Odds ratios for increased risk of mortality during childhood associated with LBW

Age	Odds ratio	95 % Confidence intervals	
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: Li et al. (2003)			

5.2.4.5.2 Sudden infant death risk

ESIP did not estimate the number of SID contingent on smoke exposure although there was sufficient evidence indicating a causal relationship between the two. This feature was introduced to the model in ESIP.H.

In the first year, death was defined as SID and other-cause death. The prevalence of SID was obtained from the national unexplained death statistics data (ONS, 2018e), provided in Appendix 13 and was adjusted according to the birth weight because the unexplained death data showed the SID risk was significantly higher among infants with LBW (OR=4.37, 95% CI, 3.31-5.80). The SID risk was subtracted from the all-cause mortality risk to find the other-cause mortality risk for the first year of life.

5.2.4.5.3 SID risk contingent on the severity of maternal smoking during pregnancy

Zhang and Wang (2013) reviewed studies investigating a dose-response association between SDP and the SID risk. A meta-analysis of those studies was conducted and the results were applied to the model (LS OR= 2.71 95% CI, 2.48-2.97; MS and HS OR=3.66 95% CI, 3.31-4.06). The meta-analysis is provided in Appendix 14.

After estimating the risk among LBW and NBW infants by applying the same methods explained previously, the impact of SHS by mother's partner during pregnancy was incorporated (OR= 1.49, 95% CI, 1.25-1.77) (Mitchell and Milerad, 2006).

Regarding the combined impact of smoke exposure by both parents, no evidence was identified. Therefore, it was assumed that if both parents smoked during pregnancy only mothers' smoking would increase the SID risk.

5.2.4.5.4 SID risk contingent on postnatal SHS exposure

The impact of postnatal SHS was applied after adjusting for the prenatal smoke exposure. The SID risk estimations in presence of SHS by either parents and by both parents calculated by Liebrechts et al. (2011) were used in the model.

- Postnatal maternal smoking OR= 2.67 (95% CI, 1.04-6.35)
- Postnatal paternal smoking OR= 2.41 (95% CI, 1.28-4.53)
- If both parents smoke OR= 5.77 (95% CI, 2.15-15.53)

5.2.4.5.5 Asthma risk

ESIP.H estimated the impact of smoking on asthma in childhood based on the prevalence in England, as shown in Table 5.344.

Table 5.34: Prevalence of childhood asthma

Age	Males (%)	Females (%)
0-4	2.29	1.36
5-9	11.44	7.88
10-14	19.18	14.11
15-19	22.34	18.27
Source: Public Health England (Flowers, 2010)		

ESIP adjusted the asthma risk according to birth weight; in response to the evidence showing children with LBW would have a 28% (95% CI 1.09-1.50) increased risk (Mu et al., 2014), which was also utilised in this version of the model.

To include the impact of smoke exposure by both parents during and after pregnancy the relevant evidence was sought. Burke et al (2012) analysed the impact of parental smoking on asthma. Studies included in that systematic review were searched to find any evidence on the impact of severity of SDP, SHS during pregnancy, and parental postpartum SHS on childhood asthma.

5.2.4.5.6 Asthma risk contingent on the severity of maternal smoking during pregnancy

Some studies (Jaakkola and Gissler, 2004, Yuan et al., 2003) in the review by Burke (2012) found an association between the severity of SDP and childhood asthma risk, as shown in Table 5.355. However, none of those studies considered the impact of

paternal smoking during pregnancy in addition to maternal SDP. Therefore, further evidence was sought.

Table 5.35: Odds ratios for asthma risk based on the severity of smoke exposure by mother during pregnancy

Cigs/day	OR, 95% CI	Age at measurement of asthma	Reference
<10	1.20 (1.04-1.38)	7	Jaakkola (2004)
10+	1.31 (1.09-1.58)		
1-7	1.45 (1.02-2.06)	1	Yuan (2003)
8-12	1.54 (1.13-2.09)		
≥13	2.10 (1.52-2.91)		

5.2.4.5.7 Asthma risk contingent on SHS exposure during pregnancy

One of the studies included by Burke et al. (2012) identified SHS exposure during pregnancy as a risk factor for asthma in childhood but they only reported unadjusted ORs (Kang et al., 2009). Therefore, further evidence was identified. Harju and colleagues (2016) estimated asthma risk in children aged between two and 10 by maternal and paternal smoke exposure in utero (Table 5.366). Taking a conservative approach, their estimations were also used for children younger than two, considering the impact of SDP and SHS was estimated to be higher on that group by Burke et al. (2012). However, no study was found investigating asthma risk in children aged between 10 and 15 who were exposed to SHS in utero. Hence, after the age of 10, for children exposed to SDP only or SDP and SHS during pregnancy simultaneously, the ORs for SDP reported by Burke et al. (2012) were applied.

Table 5.36: Odds ratios for asthma risk based on SHS exposure compared to those with never smoker parents

	Mother	Smoker	Quitter
Father	**Smoker**	OR= 3.74, 95% CI, 3.2-4.44	OR= 2.81, 95% CI, 2.03-3.04
	Non-smoker	OR= 1.65, 95% CI, 1.2-2.22	OR =1.17, 95% CI, 0.9-1.05

Source: Harju et al. 2016

When estimating the probabilities for children younger than 10 and exposed to SDP only, findings of the study by Harju et al. (2016) were adjusted in accordance with data provided by two studies (Jaakkola and Gissler, 2004, Yuan et al., 2003) that found a dose-response relationship between SDP and asthma. This enabled different probabilities to be assigned based on the severity of SDP. However, due to a lack of evidence, for the remaining groups (children above 10, those exposed to SDP and SHS by mother's partner) it was assumed that severity of SDP did not have any impact. The odds ratios for increased risk of asthma by age groups are provided in Table 5.37.

Table 5.37: Odds ratios for increased asthma risk by age

Age	Maternal SDP only (mother LS or MS)	Maternal SDP only (mother HS)	Maternal SDP and SHS during pregnancy	Only paternal SHS during pregnancy
1-2	1.45 (1.02-2.06)*	2.1 (1.52-2.91)*	3.74 (3.2-4.44)***	2.81 (2.03-3.04)***
3-4	1.60 (1.2-2.11)**	1.75 (1.26-2.42)**	3.74 (3.2-4.44)	2.81 (2.03-3.04)
5-6	1.60 (1.2-2.11)	1.75 (1.26-2.42)	3.74 (3.2-4.44)	2.81 (2.03-3.04)
7	1.60 (1.2-2.11)	1.75 (1.26-2.42)	3.74 (3.2-4.44)	2.81 (2.03-3.04)
10-14	1.23 (1.12-1.36)[±]	1.23 (1.12-1.36)	1.23 (1.12-1.36)	1
15	1.23 (1.12-1.36)	1.23 (1.12-1.36)	1.23 (1.12-1.36)	1

LS, MS and HS stand for light, moderate and heavy smoking
*Yuan et al (2003), **ORs by Harju et al. (2016) adjusted according to the figures by Jaakkola and Gissler (2004), ***Harju et al. (2016), [±] Burke et al. (2012)

5.2.4.5.8 Asthma risk contingent on SHS exposure in childhood

The review by Burke et al. (2012) reported an increased risk of asthma among children exposed to parental SHS in childhood. No study in the review investigated the combined impact of maternal and paternal SHS on asthma in children above five. A study by Gonzalez-Barcala et al. (2013) found that asthma risk amongst children aged six and 14 was greater when both parents smoked. Therefore, ORs reported by them were used for the 5-14 age groups. For younger children, the highest ORs (either parental or maternal) in the corresponding age group reported by Burke et al (2012)

were applied. The odds ratios for the increased asthma risk based on the SHS exposure are provided in Table 5.388.

Table 5.38: Odds ratios used in the OCC for increased asthma risk based on SHS

Age	SHS by mother only	SHS by mother's partner only	SHS by both parents
1	2.47 (0.65-9.39)*	1.34 (1.23-1.46)*	1.34 (1.23-1.46)
3	1.05 (0.88-1.25)*	1.34 (1.23-1.46)	1.34 (1.23-1.46)
5	1.35 (0.95-1.91)**	1.63 (1.22-2.19)**	1.67 (1.24-2.25)**
7	1.35 (0.95-1.91)	1.63 (1.22-2.19)	1.67 (1.24-2.25)
10	1.24 (0.88-1.76)**	1.26 (0.92-1.73)**	1.4 (1.03-1.9)**
15	1.2 (0.98-1.44)*	0.98 (0.71-1.36)*	1.2 (0.98-1.44)
*Burke (2012); ** Gonzales-Barcala (2013)			

Regarding the severity of SHS exposure, the only study in the review by Burke (2012) estimated the impact of SHS exposure in childhood by both parents on the asthma risk by the age of six found no impact of the severity of SHS exposure (Fergusson et al., 1985). Similarly, in another study, no association was found between the number of cigarettes consumed by mother and asthma risk (Alati et al., 2006). Hence, it was assumed that the severity of smoking by mother did not affect the risk of asthma in children.

5.2.4.5.9 Lower respiratory infections risk

ESIP did not include LRI although there was sufficient evidence proving a significant relationship between SDP and postnatal SHS and LRI in infancy. This was incorporated to the ESIP.H model.

The prevalence of LRI was estimated based on the number of admissions (NHS, 2018) and the number of children by different age group (ONS, 2019e, ONS, 2019a). The

estimated prevalence of LRI by age is provided in Table 5.39. Since the admissions data was not reported by gender, the same risks were applied to both.

Table 5.39: LRI prevalence among children

Age	Number of admissions for LRI*	Number of children	LRI risk	SE
<1	45,685	665,767**	0.069	0.0003
1-4	30,644	2,745,523***	0.011	0.00006
5-9	7,451	3,334,984***	0.002	0.00003
10-14	3,236	3,032,340***	0.001	0.00002

*Average of Hospital Episode Statistics data between 2012 and 2018, NHS, 2018
**Average of number of births in England for 2012-2018, Births in England and Wales, 2019
***Average of number of children at that age group between 2012 and 2018, Mid-year population estimates, 2019

As for the risk of asthma, the LRI risk was first adjusted by birth weight based on the study by Singleton et al (2009) which reported an 82% (95% CI, 75%-89%) increase in LRI risk among infants with a birth weight of lower than 2,500 grams.

5.2.4.5.10 LRI risk in infancy contingent on the severity of SDP

The studies included in the two systematic reviews (Jones et al. 2011, Jayes et al. 2016) identified by the umbrella review (Chapter 4) were searched to find any evidence about the impact of severity of SDP on LRI. Blizzard et al. (2003) reported the impact of SDP on LRI during infancy by the number of cigarettes consumed as follows.

- 10+ cigarettes per day; RR= 1.33 (95% CI, 1.02-1.73)
- 11-20 cigarettes per day; RR= 1.49 (95% CI, 1.14-1.94)
- 21+ cigarettes per day; RR= 1.54 (95% CI, 1.10-2.11)

Only two studies (Nusslain 1999; Haberg 2007) included in the systematic review by Jones et al. (2011) investigated the impact of SHS during pregnancy but the

relationship was not statistically significant. Thus, the model assumed that SHS during pregnancy had no impact on LRI.

Regarding the impact of SDP on overall LRI risk beyond infancy, no evidence was identified. Only one study by Zlotkowska (2004) estimated that children aged 9 to 11 were more likely to experience bronchitis if their mothers smoked during pregnancy (OR= 2.1 95% CI, 1.5-2.9). To incorporate that evidence in the model, the prevalence of bronchitis admissions among children aged between 9 and 11 (0.03% and 0.02%) was estimated by using the same method explained above (section 5.2.2.2) and the increased risks were applied for only that age group.

Due to a lack of evidence, it was assumed that SDP did not affect the LRI risks except the infancy and the 9-11 age groups, adopting a conservative approach.

5.2.4.5.11 LRI risk in infancy contingent on SHS in infancy

The impact of parental smoking after pregnancy was estimated by Jones et al. (2011) as follows:

- Maternal smoking only; OR= 1.58 (95% CI 1.45-1.73, 31 studies)
- Paternal smoking only; OR= 1.22 (95% CI 1.10-1.35, 21 studies)
- Maternal and paternal smoking; OR= 1.62 (95% CI, 1.38 to 1.89, 14 studies)

The impact of maternal SHS by the severity of smoking was estimated by Blizzard et al. (2003) as follows:

- 10+ cigarettes per day; OR= 1.46 (95% CI, 1.11-1.91)
- 11-20 cigarettes per day; OR= 1.62 (95% CI, 1.26-2.09)
- 21+ cigarettes per day; OR= 1.34 (95% CI, 0.93-1.87)

Since the finding for those who smoked 21 or more cigarettes contradicted with the broader evidence showing a dose-response effect of smoking, the odds ratio for the 11-20 cigs/day group was applied to heavy smokers as well as moderate smokers. This was consistent with the result of the meta-analysis by Jones et al. (2011) which reported that maternal SHS increased the LRI risk by 58%.

5.2.4.5.12 LRI risk after infancy contingent on SHS

A further literature search was conducted to identify the impact of parental SHS on LRI after the first year. One of the studies (Taylor and Wadsworth, 1987) included in the review by Jones (2011), reported the number of hospital admissions for LRI during the first five years of life in England, Wales and Scotland based on parental SHS. Their results were used to calculate the LRI risk contingent on SDP, as shown in Table 5.40.

Table 5.40: Estimated odds ratios for LRI amongst children younger than five

	Mother	Non-smoker (95% CI)	Light/Mod. smoker (95% CI)	Heavy smoker (95% CI)
Partner	Non-smoker	1	1.13 (0.75-1.70)	2.01 (1.47-2.75)
	Smoker	1.05 (0.78-1.40)	1.32 (0.94-1.86)	1.93 (1.48-2.51)

Based on those calculations, amongst children living with a heavy smoking mother and a non-smoking partner of mother the risk was higher than in those with a heavy smoking mother and a smoking partner of mother. To enable model consistency, the lowest figure (1.93) was applied to the both groups.

Regarding the SHS impact after the first five years, only a study by Zlotkowska et al. (2005) reported a 40% (95% CI 10%- 80%) increase in the bronchitis risk among pupils

aged 9-11 when exposed to smoke by mother after pregnancy. Since there was no evidence on the impact of paternal smoking, it was assumed to have no additional effect.

For children outside the two age groups (0-5 and 9-11) the model assumed that SHS did not cause any increase in the LRI risk, taking a conservative approach.

5.2.4.5.13 Health related quality of life in the OCC

ESIP.H used the utility values reported by Caroll and Downs (2009) for children with asthma (Mean=0.9, SD=0.18) which were also used in ESIP. A literature search failed to identify a UK study which measured the impact of LRI on health utilities although some studies conducted in other countries reported around 10% reduction in the quality of life scores (Jiang et al., 2013, Sarria et al., 2018, Rolfsjord et al., 2015). Therefore, it was deemed reasonable to assume LRI would have the same impact as asthma (0.9), considering the similar symptoms of the two diseases (Athanazio, 2012, Hargreave and Parameswaran, 2006)

The utilities were discounted at 3.5% annually following the guidance by NICE (2009).

5.2.4.5.14 Healthcare costs of morbidities in the OCC

As it was the case in ESIP, ESIP.H estimated the healthcare costs arising from death and the treatment of asthma. The cost of death estimated in the mother lifetime component was used for the offspring component too. The same cost was applied to SID and other-cause mortality. Regarding the cost of asthma, a literature based

treatment cost estimation conducted in ESIP was inflated to 2017/2018 prices (£1,655) and used in ESIP.H (Curtis and Burns, 2018). In addition to that, ESIP.H estimated the cost of LRI based on NHS reference costs (£1,619) (NHS, 2018). The HRG codes used to calculate the cost of LRI are provided in Appendix 15.

5.2.5 Offspring Adulthood Component

5.2.5.1 Model structure

The ESIP.H Offspring Adulthood Component (OAC) was designed very similar to the MLC except that the impact of SHS exposure was not incorporated, assuming that after the age of 16 the child would be no longer dependant on parents as it was assumed in the ESIP model. In ESIP.H the OAC consists of the following health states:

1. Offspring non-smoker, mother smoker
2. Offspring non-smoker, mother recent quitter (0-1Q)
3. Offspring non-smoker, mother stayed quit more than one year but less than two (1-2Q)
4. Offspring non-smoker, mother long-term quitter (LTQ)
5. Offspring non-smoker, mother dead
6. Offspring non-smoker, mother smoker, mother's partner smoker
7. Offspring non-smoker, mother recent quitter (0-1Q), mother's partner smoker
8. Offspring non-smoker, mother stayed quit more than one year but less than two (12Q), mother's partner smoker
9. Offspring non-smoker, mother long-term quitter (LTQ), mother's partner smoker
10. Offspring non-smoker, mother dead, mother's partner current smoker
11. Offspring current smoker
12. Offspring recent quitter (0-1Q)
13. Offspring stayed quit more than one year but less than two (1-2Q)
14. Offspring long-term quitter (LTQ)
15. Offspring dead

The adulthood component was linked to the other components through the impact of the mother's smoking on smoking uptake of the offspring until the age of 20 in the ESIP model (Jones et al. 2018), based on the evidence showing teenagers who have smoking mothers are more likely to start smoking at the age of 15 (OR=2.19, 95% CI 1.73-2.79) (Leonardi-Bee et al. 2011). That was further developed in ESIP.H through the inclusion of the impact of mother's partner's smoking (OR=1.66, 95% CI 1.42-1.94) and the impact of having both parents smoking (OR= 2.73, 95% CI 2.28-3.28) estimated by Leonardi-Bee et al. (2011).

Although studies showed that SDP had an impact on smoking uptake, parental smoking at the age of 15 was identified as an important confounder (Biederman et al., 2017, Niemela et al., 2016). Hence, it was decided to apply only the risk increase caused by parental smoking at the age of 15. The probabilities for smoking uptake were estimated by following the methods explained in Section 5.2.3.2.

5.2.6 Model Outputs

In addition to the standard outcomes of economic models (e.g. costs and QALYs) ESIP.H produces ROI estimates. In contrast to the previous version of the ESIP model, ESIP.H produces two ROI estimates: healthcare savings only as well as healthcare savings and health gains (i.e. QALYs). The ESIP.H model produces the following outcomes:

- Within pregnancy: Number of adverse pregnancy events, number of foetuses lost, incremental cost per quitter, incremental cost per QALY, incremental net benefit.
- One year after pregnancy: Number of quitters, incremental cost per quitter, incremental cost per QALY, incremental net benefit, ROI.
- Mother lifetime: Percentage with morbidity at reference age, incremental cost per quitter, incremental cost per QALY, incremental net benefit, ROI.
- Offspring childhood (up to age 15): Number of SID, percentage with morbidity, incremental cost per child, incremental cost per QALY, incremental net benefit.
- Offspring lifetime: Percentage that are ever smokers, percentage with morbidity at reference age, incremental cost per person, incremental cost per QALY, incremental net benefit, ROI.
- Mother lifetime and offspring lifetime: Incremental cost per mother and Offspring, incremental cost per QALY, incremental net benefit, ROI.
- Household: Incremental cost per household, incremental cost per QALY, incremental net benefit, ROI.

5.2.7 Uncertainty in ESIP.H

To identify uncertainty around the estimations of ESIP.H, a series of one-way sensitivity analyses and a probabilistic sensitivity analysis were designed. This section describes the sensitivity analyses. The results of sensitivity analyses are presented in Chapter 6 for an exemplar intervention.

5.2.7.1 One-way sensitivity analyses

A range of one-way sensitivity analyses were conducted. These were as follows:

A. Postpartum relapse rates: As discussed in Section 5.2.2.1, the one-year relapse rate amongst mothers (80%) was estimated based on biochemically verified relapse rate estimated in one study (Ratner et al. 1999). It was important to demonstrate the impact of this parameter on model outputs; hence, the rate was increased from 80% to 86% in the sensitivity analysis.

B. SHS exposure amongst children: As discussed in Section 5.2.4.3, the previous version of ESIP used a SHS rate (23%) very different from the one used in ESIP.H (80%), and thus it was important to vary this to 23% in the sensitivity analysis.

C. Inclusion of childhood obesity: The review in Chapter 4 identified obesity as one of the outcomes of SDP, and it was decided to include this condition in the sensitivity analysis due to an ongoing debate about its causal link with smoking. The prevalence data was obtained from the Health Survey for England (ONS, 2018c) and the risk ratios were identified through searching the references of the two systematic reviews identified by the umbrella review (Koshy et al., 2011, Messiah et al., 2012).

It was assumed that birth weight did not have any impact on childhood obesity because of existing evidence suggesting no impact of LBW on childhood obesity (Qiao et al., 2015). Although a birth weight higher than 3,500 grams was associated with increased childhood obesity it was not possible to incorporate this because the model

does not distinguish babies with a high birth weight (Qiao et al., 2015, Evensen et al., 2017).

The cost of obesity per child was obtained from a report by Greater London Authority, which estimated the direct costs per obese child in London at £31 annually (GLA, 2011).

D. Discount rate: As suggested by the NICE guidelines for economic evaluations and used the previous economic evaluations of SDP interventions (Jones et al. 2015, NICE, 2009), a 3.5% discount rate was applied for costs and QALYs in the base-case. This was altered to 1.5% in the sensitivity analysis in line with the NICE guidelines specific to the economic evaluations of public health interventions (NICE, 2013b).

5.2.7.2 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was designed to estimate the uncertainty around ESIP.H estimations. The number of iterations was decided based on the method outlined by Hatswell et al. (2018), which suggests running the model until the confidence interval (95%) of incremental net benefit does not include zero. Hence, the PSA was run by varying the number of iterations between 1,000 and 5,000, checking the results at every 1,000. The choice of distributions was based on standard methods (Briggs et al., 2006). The list of distributions used for specific parameters in ESIP.H is provided in Appendix 16. When a standard error was not available for a mean, a 10% error was applied as per standard practice (Briggs et al., 2012, Jones, 2015). For beta distributions where parameters (a, b) were lower than 2, they were adjusted to be

above 2 without changing the mean of the distribution to prevent high proportion of sampled values very close to 0 or 1 (Cooper et al., 2014a).

ESIP used an independent random sampling approach to assign the parameters different values each time. However, this method is not appropriate for ordered parameters. For example, the probability of quitting should be lower amongst heavy smokers than in moderate smokers. Thus, in ESIP.H, the difference method was applied for most of the parameters. This method required estimating the mean and variance of the logit distribution for each parameter to get the probabilistic values. For the user-entered parameters, PSA sampling was generated on a separate sheet in the model because they would change with new entries, while for the remaining parameters previously estimated values were used. For those parameters that did not require such ordering (i.e. gender of the infant) independent sampling was used.

Additionally, morbidity risks were adjusted so that the values assigned to SHS-exposed former smokers would always be lower than those assigned to light smokers. That was necessary due to the assumption that SHS had no impact on active smokers because assigning the SHS-exposed values higher than light smokers, would mean continuing to smoke would be better than quitting for those exposed to SHS.

The PSA estimates mean values with 95% confidence intervals for model outputs. Incremental costs and outcomes are presented on a cost-effectiveness plane and a cost-effectiveness acceptability curve (CEAC) which is produced, which shows the cost-effectiveness probability of an intervention at a WTP threshold. Additionally an EVPI analysis is performed to understand whether further research is needed.

5.2.8 Internal Validity of the Model

The internal validity of the model was assessed by entering extreme parameters to the model and by comparing the model outputs with the findings of ESIP. The next chapter presents the validity of ESIP.H through an economic evaluation of a SDP intervention, where the model outputs are also compared to those of ESIP.

5.2.9 Construction of ESIP.H in Microsoft Excel

ESIP.H was built using the structure of the previous version of the ESIP model by Jones (2015), which was constructed in Microsoft Excel (2010) because of the functionality of the programme, and its user-friendly interface for undertaking the model calculations. ESIP.H includes 28 worksheets. This section explains the main sheets and how ESIP.H operates.

5.2.9.1 Programme sheet

This is the main worksheet which requires the user to enter some parameters in order to conduct the model calculations. The number of user entered parameters was increased to 15 in ESIP.H from nine in ESIP, along with the significant changes to the model contents. Figure 5.9 provides a screenshot of the programme page. The following parameters are entered by the user:

1. Cohort size
2. Base year
3. Average age of mother
4. Control and intervention SHS rate

5. Control and intervention quit rates
6. Proportion of light, moderate and heavy smokers in control and intervention
7. Proportion of partners who smoke
8. Proportion of partners who quit
9. Costs of comparator and intervention
10. Proportion of women who stayed abstinent at one year amongst those who quit at delivery
11. Proportion of partners who stayed abstinent at one year amongst those who quit at delivery
12. Discount rate for costs and QALYs (initially set to 3.5%)
13. Proportion of males amongst infants (initially set to 51%)
14. A reference age for the model to calculate the outputs of MLC (initially set to 100)
15. Probability of SHS in

- Households where mother LS or MS but partner does not smoke (initially set to 65%)
- Households where mother HS but partner does not smoke (initially set to 93%)
- Households where partner smokes but mother does not smoke (initially set to 65%)

5.2.9.2 Main model sheets

ESIP.H includes four main sheets in addition to several sheets where the data required to populate the model is preserved. The four main sheets are:

1. Comparator (Deterministic): Linked to deterministic PLC (comparator), includes the decision tree, WPC, MLC, OCC and OAC for comparator and uses deterministic values.

2. Experimental (Deterministic): Linked to deterministic PLC (experimental), includes the decision tree, WPC, MLC, OCC and OAC for intervention and uses deterministic values

3. Comparator (Probabilistic): Linked to probabilistic PLC (comparator), includes the decision tree, WPC, MLC, OCC and OAC for comparator and uses probabilistic values

4. Experimental (Probabilistic): Linked to probabilistic PLC (experimental), includes the decision tree, WPC, MLC, OCC and OAC for intervention and uses probabilistic values.

Cohort size (women)	1000
Year of pregnancy	2014
Age of mother	27
Male	0.51

QUIT RATES AT END OF PREGNANCY	Mean	Standard error
Overall Quitrate in comparator (usual care/control/background)	0.02	0.01
Overall Quitrate in intervention	0.05	0.02
Comparator		
Secondhand smoke (SHS)exposure rate	0.67	0.03
Quitrate among SHS exposed	0.00	0.00
Proportion of light smokers amongst SHS exposed	0.00	0.00
Proportion of moderate smokers amongst SHS exposed	0.00	0.00
Proportion of heavy smokers amongst SHS exposed	0.00	0.00
Quitrate among SHS UNexposed	0.00	0.00
Proportion of light smokers amongst SHS UNexposed	0.00	0.00
Proportion of moderate smokers amongst SHS Unexposed	0.00	0.00
Proportion of heavy smokers amongst SHS Unexposed	0.00	0.00
Proportion of SHS exposed children when mother LS/MS partner not smoker	0.00	0.00
Proportion of SHS exposed children when mother HS partner not smoker	0.00	0.00
Proportion of SHS exposed children when both parents smoke	0.00	0.00
Intervention		
Secondhand smoke (SHS)exposure rate	0.67	0.03
Quitrate among SHS exposed	0.00	0.00
Proportion of light smokers amongst SHS exposed	0.00	0.00
Proportion of moderate smokers amongst SHS exposed	0.00	0.00
Proportion of heavy smokers amongst SHS exposed	0.00	0.00
Quitrate among SHS UNexposed	0.00	0.00
Proportion of light smokers amongst SHS UNexposed	0.00	0.00
Proportion of moderate smokers amongst SHS Unexposed	0.00	0.00
Proportion of heavy smokers amongst SHS Unexposed	0.00	0.00
Proportion of SHS exposed children when mother LS/MS partner not smoker	0.00	0.00
Proportion of SHS exposed children when mother HS partner not smoker	0.00	0.00
Proportion of SHS exposed children when both parents smoke	0.00	0.00

Partners smoking behaviour	Mean	Standard error
Proportion of smoking partners (comparator)	0.67	0.03
Proportion of partners who quit during pregnancy (comparator)	0.03	0.00
Proportion of never smoking partners & no-partner (comparator)	0.30	0.00
Proportion of smoking partners (intervention)	0.67	0.03
Proportion of partners who quit during pregnancy (intervention)	0.03	0.00
Proportion of never smoking partners & no-partner (intervention)	0.30	0.00

Costs	Mean	Standard error
Cost (Comparator_cost_SHSexposed)	£0	£0.00
Cost (Comparator_cost_SHSunexposed)	£0	£0.00
Cost (Intervention_cost_SHSexposed)	£3	£0.30
Cost (Intervention_cost_SHSunexposed)	£3	£0.30

Discount rate costs	0.035
Discount rate QALYs	0.035
Ceiling ratio	30000

ABSTINENCE RATES ONE YEAR AFTER DELIVERY
Comparator
SHS exposed
Proportion remained abstinent given quit during pregnancy
Proportion quit smoking postpartum although smoked (LS) during pregnancy
Proportion quit smoking postpartum although smoked (MS) during pregnancy
Proportion quit smoking postpartum although smoked (HS) during pregnancy
SHS UNexposed
Proportion remained abstinent given quit during pregnancy
Proportion quit smoking postpartum although smoked (LS) during pregnancy
Proportion quit smoking postpartum although smoked (MS) during pregnancy
Proportion quit smoking postpartum although smoked (HS) during pregnancy
Intervention
SHS exposed
Proportion remained abstinent given quit during pregnancy
Proportion quit smoking postpartum although smoked (LS) during pregnancy
Proportion quit smoking postpartum although smoked (MS) during pregnancy
Proportion quit smoking postpartum although smoked (HS) during pregnancy
SHS UNexposed
Proportion remained abstinent given quit during pregnancy
Proportion quit smoking postpartum although smoked (LS) during pregnancy
Proportion quit smoking postpartum although smoked (MS) during pregnancy
Proportion quit smoking postpartum although smoked (HS) during pregnancy
Partners (Comparator)
Proportion restarted smoking given quit by delivery (woman does not smoke)
Proportion restarted smoking given quit by delivery (woman smokes)
Partners (Intervention))
Proportion restarted smoking given quit by delivery (woman does not smoke)
Proportion restarted smoking given quit by delivery (woman smokes)

Figure 5.9: ESIP.H model programme sheet

5.3 DISCUSSION

In response to the evidence suggesting that the smoking status of partner and the severity of smoking are significant determinants of quitting behaviour, this study incorporated those into an economic model for the first time by using the best available evidence. However, there are some limitations to be acknowledged. This section explains the main differences between the ESIP.H model and ESIP and identifies the limitations of ESIP.H, followed by a discussion on some potential future work.

5.3.1 Within Pregnancy Component

5.3.1.1 What is different in ESIP.H compared to ESIP?

This study improved the WPC of the ESIP model in several ways. Firstly, by grouping pregnant women as SHS exposed and SHS-unexposed, ESIP.H is capable of capturing the impact of partners' smoking status on the probability of women's quitting and on health outcomes. This is especially important for assessing public health interventions aiming to create smoke-free households.

Another improvement to ESIP is the inclusion of the severity of smoking. There is evidence showing a relationship between the number of cigarettes consumed daily and the risk of several health conditions; hence reduction is an important achievement for women who cannot quit entirely. ESIP.H allows assessment of the impact of SDP interventions in terms of reducing smoking in addition to quit rates.

ESIP.H uses different risks for former smokers when estimating the probabilities for ectopic pregnancy, miscarriage and stillbirth, while ESIP did not distinguish former smokers from non-smokers, assigning pregnant women who quit the risk ratios estimated for non-smokers. For the remaining conditions, however, the assumption of no difference between former smokers and non-smokers remained unchanged due to the umbrella review (Chapter 4) and the additional literature search failing to determine any data.

Additionally, ESIP.H used risk ratios reported in the most recent meta-analyses where possible (i.e. stillbirth, miscarriage, preterm birth), as opposed to individual studies or less comprehensive meta-analyses used in ESIP. However, there were some conditions (placenta previa, placental abruption, pre-eclampsia, LBW) for which the identified meta-analyses did not analyse the dose-response impact of SDP. In these cases, the results of observational studies were used to estimate the parameters for different smoking groups (light, moderate and heavy). However, this had no significant impact on the estimations because the overall probabilities estimated for smokers by using risk ratios reported in the meta-analyses and the original studies were similar, such as the odds ratios for placenta previa reported by Aliyu (2011) (1.50, 95% CI, 1.39-1.61) and Shobeiri and Jenabi (2017) (1.42, 95% CI, 1.3-1.54).

5.3.1.2 Limitations of the within-pregnancy component

5.3.1.2.1 Behaviour change

ESIP.H assumes that women who do not have partners have the same probability of quitting as those who have non-smoking partners. However, some studies have found that single mothers are more likely to smoke and less likely to quit than married ones (Graham et al., 2010, Kiernan and Pickett, 2006, Prady et al., 2012, Siahpush, 2004, Smedberg et al., 2014). Thus, the model might be overestimating quit rates. However, of the families with dependent children in England , the proportion of lone parents with dependent children (21%) is lower than both-parent or co-habiting couple families (79%), and thus the effect of this assumption would be limited.

The model starts with grouping women according to their smoking status at delivery time, assuming that there is no difference between women who remained abstinent throughout pregnancy and those who quit early. The assumption is justified because the studies that were identified through the umbrella review and the further literature search found no difference between the two groups (Agutu, 2012, Nicoletti et al., 2014, Rumrich et al., 2016, Pineles et al., 2014). Additionally, grouping women based on their smoking status at delivery means assuming there is no difference between women who remain abstinent for most of pregnancy and relapse near delivery and those who smoke throughout. That is a conservative and reasonable assumption because there is no evidence on the issue. However, that suggests the model might be underestimating the benefits of cessation.

Furthermore, the model does not include the impact of unintended pregnancy although there is evidence showing women are more likely to continue smoking, and less likely to reduce smoking if the pregnancy is unplanned (Cooper et al., 2017, Chisolm et al., 2014, Smedberg et al., 2014). This might affect model estimations given that around one third of full-term pregnancies are unplanned in England (Wellings et al., 2013). However, the impact of this on model outcomes is not clear because if SDP interventions are less effective in this group, the model would be overestimating the benefits of SDP interventions. On the other hand, if SDP interventions are more effective among those who have unintended pregnancies, the model would be underestimating the benefits.

5.3.1.2.2 Health outcomes

Firstly, the model assumes that SHS affects only two pregnancy-related conditions (miscarriage and placental abruption). This is limited evidence suggested that partners' smoking did not have any impact on pre-eclampsia (Parazzini et al., 2003) and no evidence was identified for the other conditions (ectopic pregnancy, placenta previa). Therefore, the model might be underestimating the morbidity burden for those conditions. However, if new evidence becomes available it could easily be incorporated into the model.

Additionally, the model makes a conservative assumption about the impact of SHS on placental abruption and stillbirth to enable consistency within the estimations by applying the risks estimated for light smokers to SHS-exposed non-smokers, which are lower than the risks reported for SHS-exposed. That is because the sources of those

risk estimations are different and applying them would result with current smokers having a lower risk than SHS-exposed non-smokers. Hence, the model potentially underestimates the impact of SHS on abruption and stillbirth.

The potential confounding of former smoking when measuring the impact of SHS is important to note. Among studies measuring the impact of SHS, only one (Pineles et al., 2014) explicitly stated that they excluded former smokers while the others (Pineles et al., 2016, Tikkanen et al., 2006, Cui et al., 2016) did not discuss this issue. If those studies did not exclude former smokers, this would result with underestimating the impact of SHS on non-smokers.

The model assumes that former smoking does not have any impact on placenta previa, abruption, pre-eclampsia, LBW, and prematurity. The evidence suggests that there is no difference in birth weight among the infants of non-smoking women compared to those born to former smokers (Parazzini et al., 2003). Thus, the assumption is appropriate for LBW but for the remaining conditions the model might be overestimating the benefits of cessation by treating former smokers as never smokers for those conditions; except for the risk of pre-eclampsia which is found to reduce with exposure to active smoking (Aliyu et al., 2011). However, the design of the model allows new evidence on that to be incorporated easily when it becomes available.

Since, there is no recent utility estimation for smokers this version of ESIP uses the same utility tariffs. Jones (2015) preferred the values estimated by Maheswaran (2013) over those reported by Kind et al. (1999) because of having a more relevant study setting (England in the former and UK in the latter) and a considerably higher number

of participants (14,117 vs. 3,395). A further justification from the perspective of ESIP.H is that the Maheswaran tariff includes values contingent on the severity of smoking while the study by Kind et al. (1999) does not. However, as stated by Jones (2015), using England-based utilities would limit the generalisability of the model findings to the UK.

Another limitation is the lack of evidence on the impact of SHS on health utilities. The model uses the same utilities for SHS-exposed and unexposed women. Similarly, due to lacking data on the impact of pregnancy itself and the pregnancy-related complications on utilities, it is assumed that experiencing those conditions does not affect quality of life. Thus, the model potentially underestimates the impact on utilities. However, new evidence could be incorporated if becomes available.

With respect to healthcare resource use, the model uses the costs calculated based on recommendation by a midwife and the NHS Reference Costs (2018) in the scarcity of data. This might have resulted in some resource use not being captured, such as hospital visits. Another related issue is that the model assigns a cost figure for all premature babies and another one for full-term babies independent of birth weight. However, in reality, LBW premature infants might require a longer stay or more intense treatment, resulting with higher costs compared to others. These could mean that the model is underestimating the costs. However, as soon as new data is available these could be updated.

The omission of birth defects and neonatal death that were found to have a causal relationship with SDP (Section 4.3.11) should be considered. The ESIP.H model might

potentially be underestimating the benefits of SDP interventions by not including those conditions. There are many different types of birth defects and the impact of SDP varies from one to another, and the most recent systematic review (Nicoletti et al., 2014) reported only a small increase in risks when all birth defects were combined (OR= 1.18, 95% CI, 1.14-1.22, 188 studies). Additionally, skin defects are reported to be lower among SDP exposed infants (OR= 0.82, 95% CI, 0.75–0.89, 5 studies)(Hackshaw et al., 2011). Regarding neonatal death, Pineles et al. (2016) found an increased risk amongst infants exposed to maternal SDP (RR= 1.22, 95% CI, 1.14-1.30, 28 studies). However, considering the low incidence of those conditions in the general population, the impact of excluding them would not be significant.

Finally, weight gain after smoking cessation was not included in ESIP.H. A meta-analysis estimated that individuals who quit smoking gain on average 5kg within 12 monhts after quitting (Aubin et al., 2012). There is limited evidence on weight gain amongst prengant smokers who quit; two trials reported that women who quitted smoking gained on average 1.7kg and 2.4kg respectively (Hulman et al., 2016, Llambi et al., 2017). In a large cohort study, excessive maternal weight gain during pregnancy was found to be related to an increased risk of cesearan section and being born large for gestational age (Nohr et al., 2008). However, the relationship was not significant if the weight gain was lower than 10kg. Due to the absence of data showing the impact of weight gain on the health risks, this was not included in ESIP.H. However, this is unlikely to have a significant impact on the outcomes.

5.3.2 Mother Lifetime and Partner Lifetime Components

5.3.2.1 What is different in ESIP.H compared to ESIP?

This study developed the MLC in several ways. Firstly, the inclusion of a new component, PLC, allows ESIP.H to capture impact of partner behaviour on women's smoking and on morbidity and mortality prevalence.

The second improvement is incorporating the impact of the severity of smoking. This is important for two reasons; first, the probability of quitting is greater among light and moderate smokers compared to heavy smokers, and second, morbidity and mortality risks differ based on the severity of smoking. Therefore, ESIP.H is capable of providing a more accurate estimation of the impacts of smoking.

Additionally, ESIP.H allows the user enter specific postpartum abstinence rates, which was not possible with ESIP. This is an important feature that enables evaluating the impact of long-term SDP interventions. If no postpartum abstinence rates are entered ESIP.H applies a generic value of 20% which was estimated based on biochemically verified measurements (Ratner et al., 1999). In contrast, ESIP utilised 53% abstinence at one year based on a systematic review which included self-reported data (Jones et al. 2016). Hence, ESIP.H uses a more reliable one year abstinence probability than ESIP.

Another improvement is the adjustment for competing morbidity risks in ESIP.H. Lacking this adjustment, some health states in the original ESIP model had a negative number of women because the sum of the morbidity probabilities exceeded 100%. That has been corrected in this version of the model.

Finally, ESIP.H uses more up to date data on adult smoking habits, morbidity and mortality risks. That is especially important regarding the population risks for CHD, stroke, and LC because there is a considerable difference in the dates of data collection, resulting with an important change in risks.

5.3.2.2 Limitations of the mother and partner lifetime components

5.3.2.2.1 Behaviour change

There is very limited evidence on postpartum relapse rates amongst mothers and partners (Jones et al. 2016). Thus, one year relapse probability in mothers who quit smoking at delivery was estimated based on two studies reporting the biochemically verified abstinence six months after delivery and one study reporting verified abstinence one year after delivery (Gielen et al., 1997, Hajek et al., 2001, Ratner et al., 1999). Similarly, the probability in partners was assumed to be the same as mothers. Those would not have a significant impact on the evaluation of short-term interventions. However, the evaluation of long-term interventions would be affected by them. If relapse rates are higher the model would be underestimating the benefits of long-term cessation interventions and on the other hand if the rates are lower the model might be overestimating the benefits of such interventions. That could be improved once new evidence becomes available.

The probability of quitting one year after delivery amongst mothers who smoked throughout pregnancy (0.13) was higher than the quitting probability at delivery (0.09). It should be noted that the former was based on self-reported data in the absence of

bio-chemically verified data (HSCI, 2010a) while the latter was CO-verified (Jones, 2015). Similarly, the quit rates one year after delivery amongst the partners who smoked during pregnancy was based on self-reported data (McBride et al., 2004). Considering the self-reported quit rates at delivery are higher than the verified rates, the probability used in the model might overestimate the number of quitters one year after delivery.

The model assumes that living in a smoke-free house has the same impact as having a non-smoking partner, because the probabilities of quitting were based on the studies investigating the effects of living in a smoke-free house compared to living in a house where smoking was permitted (Hyland 2009, Messer 2009). However, regardless of the existence of a smoke-free house policy, individuals might be affected by the smoking status of their partners. Hence, individuals who have non-smoking partners might be more likely to quit than those who do not have partners or live in a smoke-free house where partners smoke outside. Therefore, the model potentially underestimates the benefits of cessation interventions. That could be amended should new evidence become available.

Another limitation exists around the adjustments of quitting probabilities specific to the first two years after delivery contingent on the severity of smoking and SHS exposure. In the paucity of data, the model uses the relative risks reported for general smoking behaviour change to adjust for the severity of smoking. Thus, if having a smoking partner and/or the severity of smoking has a greater impact on quitting immediately after having a baby compared to outside the postpartum period, then the

model might be underestimating the health benefits. However, the model design allows the user to enter the quit and relapse probabilities of mothers on the programme sheet for the first two years following delivery, otherwise, it uses constant figures.

Additionally, the impact of the severity of smoking and living with other smokers on quit rates were calculated based on a US-based study (Messer et al., 2008), and the impact of severity of smoking and living with other smokers might be different in the British population. However, a UK study investigating this relationship shows that the severity of smoking and living with other smokers have significant impact on quitting behaviour of British adults (Chandola et al., 2004). For example, the latter found that smokers living with other smokers were 65% less likely to quit and stay abstinent for at least two consecutive years during the study period of 10 years, while the former estimated that smokers living in a house where smoking was permitted were 69% less likely to quit one year later. Thus, the impact of using US-based evidence on the model estimates would be limited.

Another consideration is that the study by Hylands et al. (2009) which was used for adjusting the impact of SHS on relapse rates (except for the risks among mothers for the first year after pregnancy) reported the relapse rates in 2005 among those who lived in a smoke-free house in 2001, and 5% of the individuals living in smoke-free houses and quit in 2001 lived in houses where the smoke-free policy was removed by 2005. That suggests the relative risk of relapsing for former smokers who lived in smoke-free houses might be underestimated. Furthermore, by applying the same risks

to all former smokers, the model assumes the impact of SHS is independent of how long one individual stays abstinent. However, living with other smokers might have a greater impact during the first year following a quit attempt. That indicates the model is potentially underestimating the benefits of cessation interventions.

A further consideration is the assumptions around lifetime quit attempts; the model assumes that those who have not quit previously have the same probability as those who have quit before and that women can make endless quit attempts and relapses. However, there is evidence showing that smokers who previously tried quitting are more likely to quit in their following attempts. That means that the model is underestimating the number of quitters, and consequently the health benefits. However, Jones (2015) demonstrated the complexity of incorporating that into a Markov model, suggesting it would be very difficult to parameterise and the existing information around the required number of quit attempts to permanently quit would not be sufficient for that. Considering the size of the ESIP.H model which is around eight-fold the ESIP that difficulty remains.

Similarly, as discussed by Jones (2015), the model assumes that all long-term quitters have the same probability of relapsing, regardless of how long they have stayed abstinent due to lack of data comparing the two groups. That implies that if that assumption is wrong and quitters who stay abstinent for a long time have a lower probability of relapsing, the model might be overestimating the number of relapses, and thus underestimating the cost-effectiveness of cessation interventions. However,

even if such evidence becomes available, that would be very difficult to incorporate because of the increased complexity.

Furthermore, the model assumes that the proportion of light, moderate and heavy smokers among those who relapse would be proportionate to their rates in general population. This means ESIP.H potentially underestimates the health impacts because the proportion of heavy smokers amongst relapsers (0.51) was higher than the proportions of light and moderate smokers in one trial (Hellman et al., 1991). However, when that data was applied to the model the proportion of heavy smokers was significantly higher than of light and moderate smokers, leading to a considerable overestimation in health-related costs. Therefore, using the proportions in the general population was deemed more appropriate.

Additionally, the model assumes that women cannot transit from one active smoking state to another due to lack of data. However, in reality some smokers can reduce or increase the number of cigarettes consumed daily. Looking at the proportion of light (46%), moderate (40%) and heavy smokers (14%) in women outside pregnancy (Health Survey England, 2017) compared to the proportions among smoking pregnant women (41%, 31%, and 28% respectively) that are applied in the model (Cooper et al. 2017), the impact of smoking would be underestimated. Transition between active smoking states could be introduced if any evidence becomes available.

There is another limitation related to the smoking behaviour of the partner arising from the memoryless feature of Markov models. The model does not take into account the impact of partners' smoking status change although it considers the impact of

partners' smoking status. For example, if an individual quits smoking their partner might be more likely to quit compared to living with a partner who has never smoked. Similarly, the probability of relapsing might be higher if a partner relapses compared to living with a non-smoking partner. Therefore, the model might be underestimating the quit and relapse rates. It is hard to speculate on the implications of this on the model estimates.

In addition, due to lacking data, the model assumes that living with a smoker does not affect the probability of starting to smoke for never smoker partners. However, in reality those might be more likely to start smoking than individuals living in a smoke-free household. That limitation can easily be overcome if new evidence emerges.

5.3.2.2.2 Health outcomes

The model assumes that smoking has no impact on mortality rates among individuals younger than 35 due to a lack of evidence. In addition, because there is no study showing the impact of SHS on former smokers the increase in risks is assumed to be the same as among never smokers. However, there are two big cohort studies (Malek et al. 2015, Vineis 2005) showing that former smokers are more susceptible to the impacts of SHS on morbidity risks, which indicates that the relative risks for former smokers might be higher for mortality as well. If the risk is higher in former smokers compared to never smokers, the model would be underestimating the mortality burden caused by SHS.

Regarding the morbidity risks in general population, the model used Health Survey for England (2016) data for CHD and stroke. Because that data was reported by age groups, there were sudden changes in the morbidity risks for individuals who have just moved from one age group to another. For example, among females aged 65 to 74 the CHD risk was 5.29% while the corresponding figure for those 75 and older were 13.42%, thus between the ages 74 and 75 there was a considerable increase in the CHD risk. In reality, an individual would not experience such change in risks. However, the overall impact of this on the model outputs would be limited.

A further limitation caused by lack of data is related to the age-specific morbidity prevalence estimates based on the severity of smoking. As explained above, the risk ratios reported by the Surgeon General's Report (2014) were adjusted based on the meta-analyses instead of using the risk estimates from meta-analyses as they were. This was undertaken because the risk ratios reported in the former are higher than the figures in the latter, but the model might be overestimating the morbidity burden generated by smoking. However, the estimations by the Surgeon General's report are deemed to be more accurate owing to the larger sample size.

In addition, since the Surgeon General's estimations were conducted based on two different trials, the proportions of light, moderate and heavy smokers were different for people aged 35-54, and that was taken into account during adjustments. However, it is important to note that the proportion of heavy smokers were considerably high in the trial that was used for the 35-54 age group. Therefore, the relative risk estimates for that age group was lower than the other age groups.

In the base-case, the model assumes that all women who have smoking partners are exposed to SHS. Therefore, it is arguable that the impact of SHS on health outcomes is overestimated. However, considering that 80% of children with smoking parents had detectable nicotine levels (Health Survey England, 2017) non-smoking adults living with a smoker are very likely to be exposed to SHS. Therefore, it is reasonable to assume that all women are SHS-exposed if they have smoking partners. Moreover, the model design allows the user to enter different values for SHS exposure and the proportion of smoking partners. Hence, if this information is available, ESIP.H would be able to provide a more accurate estimation.

Another consideration is the potential confounding of SHS-exposure on the impact of active smoking. Only one of the meta-analyses (Hackshaw et al., 2018) which examined the impact of active smoking discussed whether their control groups included women who were exposed to SHS. Hackshaw et al. (2018) noted some studies might have included women exposed to SHS in the control groups, which means the impact of active smoking on CHD would have been underestimated. Since none of the other meta-analyses explicitly stated if they excluded women who were exposed to SHS, the same underestimation risk applies to COPD, LC and stroke as well.

When adjusting the quitting probabilities based on the impact of living with as smoking partner, an average SHS rate reported in two trials (0.33) was used (Messer et al. 2009, Hyland et al. 2009) in the absence of a national figure. That assumption is appropriate because the nicotine-validated SHS rate among non-smokers is 0.28 for males and 0.24 for females (ONS, 2018b) and the figure is expected to be higher among smokers.

However, if the actual figure is higher than 0.33 then the model would be underestimating the cost-effectiveness of SDP interventions.

Nearly all meta-analyses reporting increased morbidity risks caused by SHS, reported the impact of SHS by partner on never smokers only (excluding former smokers), just one review by Oono et al. (2011) included six original studies which included former smokers and never smokers in their control groups, and three studies that assessed workplace SHS. Thus, the impact of SHS on stroke might have been underestimated, due to a lack of data.

Regarding the impact of SHS, Lee et al. (2017) and Lee et al (2018) estimated the risks by gender but that analysis included SHS from other sources (i.e. workplace); the analysis which excluded other SHS sources was not conducted by gender. Therefore, the overall figures were used in the model.

In relation to the quality of life estimations, SHS is assumed to have no impact on health utilities due to a lack of research in a UK setting. Since studies from other settings shows that SHS reduces quality of life, ESIP.H might be underestimating the impact of SHS on quality of life. However, if new evidence becomes available that could easily be incorporated.

Finally, the morbidities in the model (childhood asthma, CHD, COPD, LC and stroke) were assumed to be associated with one-off costs only, whereas there are likely to be ongoing costs. The cost of stroke was estimated to occur over a five year period after a stroke (Youman et al. 2003) as studies have found that costs after this period are limited (Gloede et al., 2014). In addition, as life expectancy is very low for patients with

LC (ONS, 2019b), assuming a one-off cost for this condition was seen to be appropriate (European Respiratory Society, 2014) and in the line with other studies (Jones 2015). However, for CHD and COPD, the omission of recurring costs means that ESIP.H potentially underestimates the benefits of SDP interventions.

5.3.3 Offspring Childhood and Adulthood Components

5.3.3.1 What is different in ESIP.H compared to ESIP

The OCC in ESIP.H developed the childhood component in ESIP. in several ways. First, the inclusion of SHS during pregnancy and the number of cigarettes consumed by the mother affects the morbidity risks in childhood. For instance, children whose mothers were light smokers during pregnancy have a lower risk of being diagnosed with asthma compared to those who have heavy smoking mothers during pregnancy.

Secondly, ESIP.H incorporates SHS by both parents in childhood, which has a significant impact on SHS exposure and morbidity risks. For example, in ESIP.H, children are more likely to be exposed to SHS if both parents smoke compared to when only the mother smokes.

Another significant improvement is using more recent SHS exposure data from a national survey which bio-chemically verified the risk among children who had smoking parents. ESIP used a significantly lower probability for being exposed to SHS by parents (23% vs. 80%), and the figure used in ESIP was based on self-reported data.

Thus ESIP.H uses a more reliable data on the probability of SHS exposure amongst the children of smoking parents.

A further improvement to ESIP is related to asthma risks. ESIP assumed that the probability of asthma was the same for children whose mothers did not smoke and those whose mothers had quit prior to or during pregnancy. ESIP.H partly overcomes this by applying the figures reported by Harju et al. (2016), which indicated a 17% increase for the latter. However, there was no evidence on that for children older than 10, and the probabilities for never-smokers were applied to those above 10 as it was the case in ESIP. In addition, ESIP.H captures the impact of SDP and SHS on SID and LRI, which were not estimated in ESIP.

The OAC in ESIP.H considers the impact of severity of smoking, which was not considered in ESIP, in addition to using more recent smoking, mortality and morbidity data.

5.3.3.2 Limitations of the offspring components

A limitation of the OCC is that when both parents smoke, the probability of SHS exposure is related to mother's smoking only. This means, the severity of partner smoking would not have any impact on the SHS exposure probability. Thus, for example a light smoker mother and heavy smoker partner would have the same probability of exposing their children to SHS as a light smoker mother and light smoker partner. As a result, ESIP.H potentially underestimates the SHS risk and hence the benefits of cessation interventions.

Also, the model does not consider the impact of the severity of partner smoking on the probability of SHS or health outcomes on children. The impact of this would be dependent on the severity of smoking among partners in a specific intervention and cohort. If an intervention reduces the number of cigarettes consumed by partners, the ESIP.H model would not be able to capture the impact of that on SHS exposure or health outcomes.

The model assumes that if both parents smoke during pregnancy SHS by partner during pregnancy has no additional impact on SID due to a lack of data on the combined impact of SDP and SHS during pregnancy. However, one study found a significantly increased risk of SID when both parents smoke after pregnancy compared to when only mother smokes (Liebrechts-Akkerman et al., 2011). Thus, ESIP.H potentially underestimates the SID risk. On the other hand, since the prevalence of SID is very low the impact of this on the model results would be limited.

A further consideration is the assumption that mother's smoking just before or in the beginning of pregnancy would not increase the risk of SID or LRI although it increases the risk of asthma (Harju et al., 2016) due to a lack of evidence for SID and LRI. Similarly, due to the absence of data, the model assumed that SDP does not have any impact on the LRI risk except for infants and children in the 9-11 age groups. Thus, ESIP.H potentially underestimates the risk of SID and LRI.

Another potential underestimation exists around the asthma risk calculations. The model assumes that after the age of 10, paternal SHS during pregnancy has no impact on the childhood asthma risk, although SDP increases the risk by 23%. Similarly,

regarding the impact of SHS in childhood, the model uses the highest ORs (either maternal or paternal) in the absence of risk estimation for the impact of SHS by both parents amongst children younger than five and those aged 15. Thus, ESIP.H potentially underestimates the risk of asthma. This could be updated when new evidence becomes available.

Additionally, the impact of LRI on health-related quality of life is assumed to be the same as asthma because the literature search failed to identify any UK-based study with relevant data. That is justified by the evidence from other countries and the similar nature of the two conditions. However, if this assumption is wrong and LRI has a lower impact on health-related quality of life, ESIP.H would be overestimating the impact of smoking, and if LRI has a higher impact it would be an underestimating the health impacts. This parameter could be updated when new evidence becomes apparent.

Furthermore, the prevalence of LRI risk in the general population was estimated based on national hospital admissions in the absence of a prevalence data. If the actual prevalence of LRI is lower, ESIP.H would be overestimating it, whereas if the prevalence is higher the model results would be overestimating the LRI risk. However, ESIP.H uses the best available evidence in order not to ignore the impact of SDP and SHS on the LRI risk and new data could easily be incorporated once it is available.

Since the OAC uses the same smoking behaviour change and morbidity risk parameters as in the MLC and PLC limitations discussed for those components apply to the OAC too. Additionally, the OAC model does not consider the impact of SHS on morbidity

risks although 26% of non-smokers (ONS, 2018a) and around 33% of smokers are exposed to SHS (Messer et al., 2008, Hyland et al., 2006). Therefore, ESIP.H potentially underestimates the impact of SHS. However, since the focus of ESIP.H is the household, not including other sources of SHS seems reasonable.

5.3.4 Potential Future Improvements to ESIP.H

Key improvements to ESIP.H would be possible once better data is available for postpartum abstinence rates and long-term relapse rates. Similarly, more evidence on the impacts of SHS on quit behaviour and mortality risks and health-related quality of life would benefit the model to produce more accurate results.

Additionally, it is possible to improve the model further by incorporating e-cigarette use. This could be done by introducing another health state to the lifetime models. Although the evidence around e-cigarette use during pregnancy is very limited they are widely used as a cessation aid. Recent research shows that e-cigarettes include 95% less harmful chemicals (McNeill et al., 2018). Currently there is no study showing the impact of e-cigarette use on pregnancy-related conditions and it is not clear whether 95% reduction in harmful materials would mean 95% decrease in risks (McNeill et al., 2018). However, it is possible to model the effects of different assumptions (e.g. 30%-50% decrease in risks). One potential problem would be the position of e-cigarette users in comparison with former smokers; this could be overcome by assigning e-cigarette users higher values than former smokers. Furthermore, switching to e-cigarettes would mean a significant reduction in the impacts of SHS for children. For

example, one study estimated that nicotine levels in homes with smokers are 5.7 times of the levels in homes with e-cigarette users (Ballbè et al., 2014). Hence, the inclusion of e-cigarettes would require many assumptions due to the lack of data. However, if more evidence becomes available on the effects of e-cigarettes in near future this would enable the researchers to obtain more accurate parameters for the model.

Another potential improvement would be considering the impact of socioeconomic status since SDP is more common among disadvantaged women. There is some evidence showing the increased impact of smoking on morbidities among people from lower socioeconomic groups, such as placental abruption, perinatal death, LBW, and childhood asthma (Kyrklund-Blomberg et al., 2001, Silvestrin et al., 2013, Kang et al., 2009, Lundsberg et al., 2015). For example, one meta-analysis concluded that a high level of maternal education provided 33% protection against LBW compared to low level maternal education (Silvestrin et al., 2013). Additionally, the probability of quitting is affected by one's socioeconomic status. Furthermore, in the lowest income group, non-smokers are more likely to be exposed to SHS (ONS, 2018b). Hence, incorporating this into the model would be a significant enhancement in order to estimate the impact of SDP on health inequities. The most straightforward way of doing this would be re-parameterising two versions of the model; one for a higher socioeconomic group and one for a lower socioeconomic group. That is because incorporating this as a component of the same model would generate computational issues due to the model size.

5.4 CONCLUSION

The ESIP.H model was constructed by improving an existing model called ESIP. The new model has the potential to produce more accurate estimates of the impacts of interventions to address SDP. ESIP.H is the first smoking cessation model to consider the impact of partner smoking and the severity of smoking. In addition to being able to estimate the impact of smoke-free household interventions, this model enables the incorporation of the spill-over effects of SDP interventions that target only women and allows analysis of the impacts of reducing smoking among those who are not ready to quit.

5.5 CHAPTER SUMMARY

This chapter explained how the ESIP.H model was developed. The ESIP.H model is different from the previous models because it is the first to incorporate partner smoking and the severity of smoking. The next chapter presents the results of an economic evaluation of a SDP intervention using ESIP.H, and compares its findings to those of ESIP.

CHAPTER 6: EVALUATING MiQUIT INTERVENTION USING ESIP.H

6.1 INTRODUCTION

The previous chapter explained the development of a decision analytic model (ESIP.H) for SDP interventions. This chapter demonstrates the use of ESIP.H by evaluating a SDP intervention named MiQuit which was previously evaluated by Jones (2018) using ESIP. This study aims to demonstrate the use and validity of ESIP.H by comparing the outputs of ESIP.H to those of ESIP.

6.1.1 The MiQuit Trial

The MiQuit trial was a randomised controlled trial of a tailored text messaging intervention to help smoking pregnant women quit (Naughton et al., 2017). Participants consisted of 407 women who were at least 25 weeks pregnant. The intervention group received 12-week cessation support via text-messages in addition to the standard NHS service delivered to the control group. The messages were tailored according to the specific features of individuals, such as motivational status, gestational age, barriers to quit and partner's smoking. Women were able to alter the frequency of messages and were encouraged to set a quit date to get support specific

to their stage. Full details of the trial were published by Naughton et al. (2017). Tailoring methods and example messages are presented in Appendix 17.

The women were followed until 36 weeks gestation when biochemically validated continuous quit data was collected. In the intervention group 11 of 203 women and in the control four of 204 women had quit at 36 weeks gestation.

6.2 METHODS

The economic evaluation methods outlined in Chapter 3 were used to estimate the incremental cost per quitter, incremental cost per QALY and incremental net benefit (INB). Additionally return on investment analyses (ROI) were conducted for different time horizons (one year after delivery, mother and offspring lifetime, and household lifetime). The ROI analyses included estimating two different benefit-cost ratios, one covering the NHS healthcare cost savings only (ROI1) and the second capturing health gains as well (ROI2), where a QALY was assigned a monetary value of £30,000 in keeping with the incremental net benefit analyses conducted by Jones (2015).

The inputs obtained from the published paper on MiQuit are shown in Table 6.1 (Naughton et al., 2017). Although the number of participants was 407 in the trial, Jones et al. (2018) used a cohort of 1,000 women in their estimations. Hence the cohort size was set as 1,000 to enable comparability between the two estimates.

Table 6.1: Model inputs for evaluating the MiQuit intervention

Input	Value (SE)
Cohort size	1000
Birth year	2014
Age of mother	27
Proportion of smoking partners in control	0.67 (0.3)
Proportion of smoking partners in intervention	0.67 (0.3)
Proportion of quitters in control	0.02 (0.01)
Proportion of quitters in intervention	0.05 (0.02)
Cost of control	£0.00
Cost of intervention	£3.04 (0.3)

Naughton et al. (2017) reported a higher proportion of partners smoking in the intervention group (0.67) than in the control (0.63) at enrolment. However, this parameter was not collected at follow-up and thus there was no data showing the impact of the intervention on partners. Applying those figures would imply that the intervention increased the SHS rates although it was very unlikely to have such impact since partners were not included in the MiQuit intervention. Therefore, it was decided to use the same figure for both groups (0.67).

To enable a comparison between the findings of ESIP.H and ESIP 2014-2015 prices were used for the costs accrued related to health conditions. The healthcare costs included in the model are provided in Table 6.2.

Table 6.2: Healthcare costs included in the evaluation of MiQuit intervention

Cost component	Cost (2014-2015)	SE	Source
Ectopic	£578.07	226.31	Jones (2018)
Miscarriage	£578.07	226.31	Jones (2018)
Abruption & Previa	£1,202.38	559.71	Jones (2018)
Pre-eclampsia	£657.89	329.60	Jones (2018)
Premature birth	£1,224.04	521.77	Jones (2018)
Community Midwife Visit	£55.51	17.29	Jones (2018)
Obstetrician First Visit	£146.38	68.31	Jones (2018)
Obstetrician subsequent visit	£113.90	62.86	Jones (2018)
Standard Ultrasound scan	£110.77	60.65	Jones (2018)
Specialised Ultrasound Scan	£131.81	50.98	Jones (2018)
Normal birth	£2,497.05	745.03	Jones (2018)
Emergency Caesarean Section	£4,180.54	1,214.01	Jones (2018)
Caesarean Section	£3,781.28	1,072.94	Jones (2018)
Routine Observation	£345.24	206.71	Jones (2018)
Death	£1,630.98	854.11	Jones (2018)
Stillbirth	£1,063.28	676.26	Jones (2018)
Neonatal care Premature	£15,934.55	7,127.79	Jones (2018)
Neonatal care Full term	£2,645.87	2,423.44	Jones (2018)
CHD	£1,838.62	183.86	Jones (2018)
COPD	£843.65	84.37	Jones (2018)
Lung cancer	£9,554.98	955.50	Jones (2018)
Stroke	£21,724.88	147.96	Jones (2018)
Asthma	£1,624.00	162.40	Jones (2018)
LRI	£1,730.00	173.00	NHS (2015)
Childhood obesity	£37	0.37	GLA (2011)

6.3 ANALYSIS

Economic evaluations were conducted separately for the mother and offspring and by combining the outcomes for mother and offspring and mother, partner and offspring (household). Additionally, analyses were undertaken at different timescales (i.e. pregnancy, one year after delivery, offspring childhood and lifetime). Sensitivity analyses were performed to estimate the impact of varying certain parameters (postpartum abstinence rates, SHS exposure rate amongst children, inclusion of obesity and discount rates). Additionally, a probabilistic sensitivity analysis (PSA) was conducted.

ESIP.H adopted an NHS and PSS perspective in line with ESIP. A discount rate of 3.5% was applied to all future costs and benefits as per NICE guidelines.

6.4 RESULTS

6.4.1 Deterministic Results

Tables 6.3 and 6.4 below present the deterministic results separately for mother and offspring and Table 6.5 shows the combined results for mothers and offspring and household results which include the impacts on partners in addition to mothers and offspring. MiQuit generates 35 additional quitters at delivery amongst 1,000 mothers who are committed to quit (Table 6.3). One year after delivery, only four more women are abstinent in the intervention compared to the comparator.

According to the combined results for the mother and offspring at delivery, the MiQuit intervention is £4.63 more costly than the comparator and it produces an additional 0.0030 QALY gain. The incremental cost per QALY is £3,510 and it provides an incremental net benefit of £35 per QALY gained. Hence, the intervention is cost-effective at delivery if the decision-maker is willing to invest £30,000 per QALY. It gains dominance over the comparator when the costs and benefits one year after delivery are also considered, with an incremental net benefit of £161. The incremental net benefit increases significantly in the combined lifetime analyses to £1,189 for the mother and offspring and to £1,426 for the household.

According to the ROI analysis, MiQuit does not provide economic returns to the NHS either at delivery or one year after delivery. However, when health gains (QALYs) are also considered, it produces a return of £11.50 per £1 spent at delivery and £29.83 one year after delivery (Table 6.5). Moreover, in the lifetime analyses the amount of return per £1 increases to £391 for the mother and offspring and to £469 for the household.

Table 6.3: Deterministic maternal outputs of ESIP.H

MATERNAL: END OF PREGNANCY			
	Comparator	**Intervention**	**Incremental**
Number of quitters	19.61	54.19	34.58
Quit rate	1.96%	5.42%	3%
Expected cost per mother	£3,100.95	£3,105.90	£4.95
Expected QALYS per mother	0.6322	0.6335	0.0013
Number of adverse pregnancy events	123.68	122.77	-0.91
		Incremental cost per QALY	£3,754.92
		Incremental cost per quitter	£143.27
		Incremental net benefit per QALY	£34.63
MATERNAL: LIFETIME			
Results at age	100		
	Comparator	**Intervention**	**Incremental**
% of cohort stillbirth alive	16.57%	16.61%	0.04%
% of cohort with morbidity	6.61%	6.62%	0.01%
Expected cost per mother	£19,867.46	£19,853.13	-£14.32
Expected Life Years	25.0092	25.0122	0.0030
Expected QALYS per mother	21.5026	21.5099	0.0073
		Incremental cost per LY	Dominant
		Incremental cost per QALY	Dominant
		Incremental cost per quitter (mother)	Dominant
		Incremental net benefit per QALY	£232.75

Table 6.4: Deterministic infant outputs of ESIP.H

INFANT: END OF PREGNANCY			
	Comparator	**Intervention**	**Incremental**
Number of infant deaths	104.20	103.20	-1.00
Number of stillbirths	5.61	5.57	-0.05
Number of infants born prematurely	69.56	69.31	-0.25
Number of infants born with LBW	102.47	100.96	-1.51
Number of adverse live births	118.75	117.39	-1.35
Number of any adverse infant outcomes	222.94	220.60	-2.35
Expect cost per infant	£3,251.24	£3,253.96	£2.72
		Incremental net benefit per adverse live birth	£37.81
		Incremental net benefit per adverse pregnancy outcome	£67.68
OFFSPRING: AGE 15 (END OF CHILDHOOD)			
	Comparator	**Intervention**	**Incremental**
Percentage alive	89.00%	89.11%	0.11%
Number of SID	1.45	1.44	-0.01
Percentage with morbidity	26.13%	26.63%	-0.50%
Expected cost per child	£7,144.75	£7,092.08	-£52.67
Expected LYs per child	10.2561	10.2681	0.0120
Expected QALYs per child	10.0179	10.0333	0.0154
		Incremental cost per LY	Dominant
		Incremental cost per QALY	Dominant
		Incremental net benefit per QALY	£515.28
OFFSPRING LIFETIME			
Results at age 100	**Comparator**	**Intervention**	**Incremental**
Percentage stillbirth alive	31.47%	31.51%	0.04%
Percentage of cohort who were ever smokers	30.28%	30.31%	0.03%
Percentage suffering from any morbidity	17.80%	17.82%	0.02%
Expected cost per person	£15,514.22	£15,471.18	-£43.05
Expected LYs per person	24.1353	24.1635	0.0282
Expected QALYs per person	22.4848	22.5152	0.0303
		Incremental cost per LY	Dominant
		Incremental cost per QALY	Dominant
		Incremental net benefit per QALY	£953.27

Table 6.5: Deterministic combined outputs of ESIP.H

ONE YEAR AFTER DELIVERY			
	Comparator	**Intervention**	**Incremental**
Number of quitters	130.19	134.57	4.37
Quit rate	13.02%	13.46%	0.44%
Expected cost per mother and infant	£6,778.80	£6,778.59	-£0.21
Expected LYs per mother and infant	2.5345	2.5361	0.0015
Expected QALYs per mother and infant	2.3380	2.3410	0.0030
		Incremental cost per quitter	Dominant
		Incremental cost per QALY	Dominant
		Incremental net benefit per QALY	£160.87
COMBINED MOTHER AND OFFSPRING: END OF PREGNANCY			
	Comparator	**Intervention**	**Incremental**
Expected cost	£6,352.19	£6,356.82	£4.63
		Incremental cost per quitter	£133.91
		Incremental cost per QALY	£3,509.71
		Incremental net benefit per QALY	£34.95
COMBINED MOTHER LIFETIME AND OFFSPRING CHILDHOOD			
	Comparator	**Intervention**	**Incremental**
Expected cost	£27,012.21	£26,942.18	-£70.03
Expected LYs	35.2653	35.2803	0.0150
Expected QALYs	31.5205	31.5432	0.0227
		Incremental cost per quitter	Dominant
		Incremental cost per LY	Dominant
		Incremental cost per QALY	Dominant
		Incremental net benefit per QALY	£751.07
COMBINED MOTHER AND INFANT: LIFETIME			
	Comparator	**Intervention**	**Incremental**
Expected cost	£35,381.68	£35,321.27	-£60.41
Expected LYs	49.1445	49.1757	0.0312
Expected QALYs	43.9875	44.0251	0.0376
		Incremental cost per quitter	Dominant
		Incremental cost per LY	Dominant
		Incremental cost per QALY	Dominant
		Incremental net benefit per QALY	£1,189.05
HOUSEHOLD: COMBINED MOTHER, PARTNER AND OFFSPRING LIFETIME			
	Comparator	**Intervention**	**Incremental**
Number of quitters at delivery	53.61	88.19	34.58
Expected cost per household	£62,680.11	£62,474.70	-£205.41
Expected LYs	73.8358	73.8758	0.0400
Expected QALYs	66.2154	66.2561	0.0407
		Incremental cost per quitter	Dominant
		Incremental cost per LY	Dominant
		Incremental cost per QALY	Dominant
		Incremental net benefit per QALY	£1,426.12

Table 6.5: Deterministic combined outputs of ESIP.H (continued)	
Healthcare costs return on investment (ROI1)	
At delivery	**-1.52**
One year after delivery	**0.07**
Mother and offspring lifetime	**19.87**
Household lifetime	**67.57**
Healthcare costs and QALY gains return on investment (ROI2)	
At delivery	**11.50**
One year after delivery	**29.83**
Mother and offspring lifetime	**391.14**
Household lifetime	**469.12**

6.4.2 One-way Sensitivity Analyses

As explained in Chapter 4, four different sensitivity analyses were designed to estimate the impact of following:

- (A) postpartum relapse rates by increasing this parameter from 80% to 86%,
- (B) SHS exposure amongst children by reducing this parameter from 80% to 23%,
- (C) inclusion of childhood obesity (ages 2-15),
- (D) discount rates by reducing it from 3.5% to 1.5%.

The impact of those parameters on incremental cost per QALY per mother and infant estimates one year after delivery and for the lifetime analyses are shown in Table 6.6 below.

Table 6.6: Incremental cost per QALY estimations of the sensitivity analyses

One-year after delivery (Mother and offspring)					
	Base-case	**A**	**B**	**C**	**D**
Incremental cost	-£0.26	-£0.13	£2.24	-£0.26	-£0.31
Incremental QALY gain	0.0030	0.0030	0.0028	0.0030	0.0030
ICER	**Dominant**	**Dominant**	**£786.41**	**Dominant**	**Dominant**
Lifetime (Mother and offspring)					
Incremental cost	-£60.41	-£57.69	-£39.34	-£61.22	-£58.88
Incremental QALY gain	0.0376	0.0369	0.0358	0.0399	0.0628
ICER	**Dominant**	**Dominant**	**Dominant**	**Dominant**	**Dominant**
Lifetime (Household)					
Incremental cost	-£205.41	-£202.69	-£184.34	-£206.22	-£392.96
Incremental QALY gain	0.0400	0.0400	0.0388	0.0429	0.0691
ICER	**Dominant**	**Dominant**	**Dominant**	**Dominant**	**Dominant**
ROI1 one year after delivery (Mother and offspring)					
	0.07	0.04	-0.47	0.07	0.10
ROI2 one year after delivery (Mother and offspring)					
	29.83	29.43	11.50	29.83	11.50
ROI1 lifetime (Household)					
	67.57	66.67	60.64	67.84	129.27
ROI2 lifetime (Household)					
	391.14	461.33	443.83	491.60	811.83

The sensitivity analyses show that none of the parameter variations or inclusion of obesity changes the cost-effectiveness of MiQuit since all estimations are below £30,000 per QALY gained. It is noteworthy that reducing the SHS exposure rate from 80% to 23% (B) has the greatest impact on the incremental results although the impact diminishes in the lifetime analyses. On the other hand, the incremental QALY gains and cost savings in lifetime analyses rise significantly with the inclusion of childhood obesity (C). Additionally, changing the discount rate from 3.5% to 1.5% (D) the intervention becomes more cost-effective. Similar patterns are observed for the ROI

estimations. Figure 6.1 below demonstrates the incremental results for the household lifetime outcomes for the one-way sensitivity analyses.

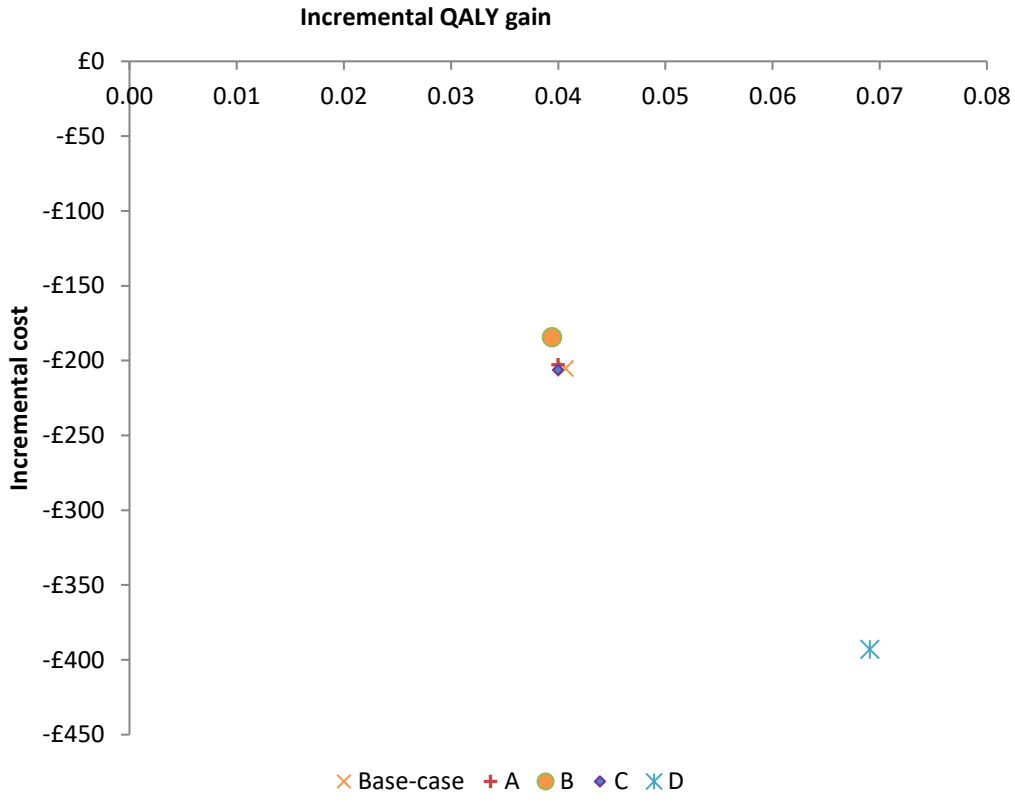


Figure 6.1: Scatterplot of the one-way sensitivity analyses for the household lifetime horizon

6.4.3 Probabilistic Sensitivity Analysis

To estimate the uncertainties around the estimations, a PSA was conducted and the model convergence was achieved with 1,000 iterations. The results for the mother and infant separately are provided in Tables 6.7 and 6.8 and the combined results in Table 6.9.

The results suggest that the MiQuit intervention is cost-effective at £30,000 WTP with an incremental cost of £3,864 per QALY when only the pregnancy outcomes are considered and it is dominant over the comparator if the effects beyond delivery are also taken into account. Similarly, the cost per quitter is £149 at delivery, which would be cost-effective if the decision-maker is willing to pay £30,000 per quitter while it gains dominance when the longer term outcomes are also considered. The incremental net benefit per QALY is £35 at delivery and it increases up to £1,451 in the household lifetime analysis.

The majority of the confidence interval estimates does not cross zero, suggesting the differences between MiQuit and the comparator are statistically significant. However, the cost per infant at delivery and the combined cost per mother and infant show that there is no significant difference between MiQuit and the comparator (£2.47, 95% CI, -3.51 to £11.46 and £4.79 CI, 95% CI, -£2.07 to £14.38 respectively).

Table 6.7: Results of the probabilistic sensitivity analysis for the offspring

	Comparator			Intervention			Incremental		
MATERNAL: END OF PREGNANCY	**Mean**	**95% CIs**		**Mean**	**95% CIs**		**Mean**	**95% CIs**	
Number of quitters	19.59	16.73	22.60	54.19	46.36	62.67	34.60	29.27	40.32
Quit rate	1.96%	1.96%	1.96%	5.42%	1.96%	1.96%	3%	3%	4%
Expected cost per mother	£3,120.61	£1,995.49	£4,729.01	£3,125.78	£2,001.94	£4,736.74	£5.17	£3.23	£7.77
Expected QALYS per mother	0.6321	0.6202	0.6427	0.6334	0.6214	0.6438	0.0013	0.0009	0.0019
Number of adverse pregnancy events	123.66	121.53	127.36	122.79	120.57	126.24	-0.86	-1.48	-0.43
					Incremental cost per QALY		£3,864.28		
					Probability cost-effective at £30,000 WTP		1.0		
					Incremental cost per quitter		£149.39		
					Incremental cost per adverse event		£5,986.99		
					Incremental net benefit per QALY		£34.96	£23.11	£49.56
MATERNAL: LIFETIME	**Mean**	**95% CIs**		**Mean**	**95% CIs**		**Mean**	**95% CIs**	
% of cohort stillbirth alive	15.75%	13.18%	19.11%	15.79%	13.23%	19.14%	0.03%	0.02%	0.05%
% of cohort with morbidity	6.43%	5.42%	7.70%	6.44%	5.43%	7.71%	0.01%	0.00%	0.02%
Expected cost per mother	£19,923.16	£18,266.27	£21,830.30	£19,912.82	£18,251.26	£21,820.83	-£10.34	-£18.22	-£2.81
Expected Life Years	24.9851	24.9062	25.0887	24.9877	24.9090	25.0909	0.003	0.0017	0.0038
Expected QALYS per mother	21.4758	21.0804	21.8170	21.4825	21.0894	21.8217	0.007	0.0041	0.0102
					Incremental cost per Life Year gained		Dominant		
					Incremental cost per QALY		Dominant		
					Probability cost-effective at £30,000 WTP		1.0		
					Incremental cost per quitter (mother only)		Dominant		
					Incremental net benefit per QALY		£210.11	£129.03	£320.31

Table 6.7: Results of the probabilistic sensitivity analysis for the offspring

	Comparator			Intervention			Incremental		
Infant: END OF PREGNANCY	**Mean**	**95% confidence interval**		**Mean**	**95% confidence interval**		**Mean**	**95% confidence interval**	
Number of foetuses lost	104.13	102.33	108.12	103.12	101.22	106.88	-1.01	-1.63	-0.57
Number of stillbirths	5.62	5.32	6.13	5.58	5.29	6.06	-0.04	-0.07	-0.03
Number of premature births	69.94	69.34	70.51	69.69	69.05	70.28	-0.25	-0.36	-0.16
Number of low birth weight infants	102.72	101.42	103.99	101.20	99.88	102.45	-1.52	-1.87	-1.20
Number of all adverse live births	119.09	117.80	120.32	117.73	116.41	118.99	-1.36	-1.67	-1.06
Number of all adverse pregnancy outcomes	223.22	220.59	226.72	220.85	218.17	224.39	-2.37	-3.13	-1.73
Expect cost per infant	£3,256.33	£898.28	£7,899.02	£3,258.80	£899.20	£7,910.56	£2.47	-£3.51	£11.46
					Incremental net benefit per adverse live birth		£40,793.50	£31,904.57	£50,141.99
					Incremental net benefit per adverse pregnancy outcome		£71,143.56	£52,011.59	£93,792.66
Offspring: AGE 15 (END OF CHILDHOOD)	**Mean**	**95% confidence interval**		**Mean**	**95% confidence interval**		**Mean**	**95% confidence interval**	
Percentage alive	88.92%	88.52%	89.11%	89.02%	88.66%	89.22%	0.11%	0.06%	0.17%
Number of SID	1.46	1.20	1.87	1.45	1.19	1.85	-0.01	-0.02	0.00
Percentage with morbidity	28.02%	24.82%	32.19%	27.45%	24.44%	31.31%	-0.57%	-1.00%	-0.29%
Expected LYs per child	10.2526	10.2083	10.2745	10.2648	10.2226	10.2864	0.0122	0.0071	0.0194
Expected QALYs per child	10.0141	9.6490	10.2052	10.0301	9.6709	10.2170	0.0160	0.0086	0.0264
Expected cost per child	£7,259.35	£4,651.07	£11,896.63	£7,198.91	£4,598.59	£11,850.45	-£60.44	-£107.71	-£26.47
					Incremental cost per life year gained		Dominant		
					Incremental cost per QALY		Dominant		
					Incremental net benefit per QALY		£540.00	£301.09	£881.27

Table 6.8: Results of the probabilistic sensitivity analysis for the offspring (continued)

OFFSPRING: LIFETIME	**Mean**	**95% confidence interval**		**Mean**	**95% confidence interval**		**Mean**	**95% confidence interval**	
Percentage stillbirth alive	30.27%	26.57%	33.52%	30.31%	26.61%	33.56%	0.04%	0.02%	0.06%
Percentage of ever smokers	27.59%	24.03%	30.76%	27.62%	24.06%	30.79%	0.03%	0.02%	0.05%
Percentage suffering from any morbidity	17.13%	15.70%	18.81%	17.15%	15.72%	18.83%	0.02%	0.01%	0.03%
Expected cost per offspring	£15,548.04	£12,860.34	£20,260.63	£15,497.24	£12,802.72	£20,175.88	-£50.79	-£98.18	-£16.83
Expected LYs per offspring	24.1017	23.9861	24.1612	24.1303	24.0219	24.1929	0.0286	0.0166	0.0455
Expected QALYs per offspring	22.5923	22.1826	22.8833	22.6235	22.2137	22.9098	0.0311	0.0178	0.0490
					Incremental cost per life year gained		Dominant		
					Incremental cost per QALY		Dominant		
					Probability cost-effective at £30,000 WTP		1.00		
					Incremental net benefit per QALY		£985.04	£574.99	£1,524.28

Table 6.8: Results of the probabilistic sensitivity analysis combined for the mother and offspring and household

	Comparator			Intervention			Incremental		
COMBINED MOTHER AND OFFSPRING: END OF PREGNANCY	**Mean**	**95% confidence interval**		**Mean**	**95% confidence interval**		**Mean**	**95% confidence interval**	
Expected cost	£6,375.93	£3,545.59	£11,439.62	£6,380.73	£3,545.73	£11,454.63	£4.79	-£2.07	£14.38
						Incremental cost per quitter	£138.50		
						Incremental cost per QALY	£3,582.68		
						Probability cost-effective at £30,000 WTP	1.00		
						Incremental net benefit per QALY	£35.34	£23.20	£50.14
COMBINED MOTHER AND OFFSPRING: ONE YEAR AFTER DELIVERY	**Mean**	**95% confidence interval**		**Mean**	**95% confidence interval**		**Mean**	**95% confidence interval**	
Number of quitters	129.59	116.28	146.56	132.59	118.98	149.42	3.00	1.04	5.23
Quit rate	12.96%	11.63%	14.66%	13.26%	11.90%	14.94%	0.30%	0.10%	0.52%
Expected cost per mother and infant	£6,813.59	£3,996.84	£11,829.88	£6,813.34	£3,992.46	£11,840.18	-£0.25	-£7.55	£9.72
Expected LYs per mother and infant	2.5346	2.5290	2.5373	2.5362	2.5307	2.5389	0.0016	0.0009	0.0025
Expected QALYS per mother and infant	2.3379	2.2995	2.3675	2.3409	2.3027	2.3703	0.0030	0.0019	0.0043
						Incremental cost per quitter	Dominant		
						Incremental cost per QALY	Dominant		
						Probability cost-effective at £30,000 WTP	1.00		
						Incremental net benefit per QALY	£90.63	£57.83	£129.45
COMBINED MOTHER LIFETIME + OFFSPRING CHILDHOOD	**Mean**	**95% confidence interval**		**Mean**	**95% confidence interval**		**Mean**	**95% confidence interval**	
Expected cost	£27,182.52	£23,956.05	£32,426.89	£27,108.89	£23,885.83	£32,381.95	-£73.63	-£124.40	-£36.66
Expected Life Years	35.2377	35.1443	35.3383	35.2525	35.1598	35.3519	0.0148	0.0090	0.0228
Expected QALYs	31.4899	30.9796	31.9095	31.5125	31.0106	31.9357	0.0226	0.0136	0.0350
						Incremental cost per quitter	Dominant		
						Incremental cost per life year gained	Dominant		
						Incremental cost per QALY	Dominant		
						Probability cost-effective at £30,000 WTP	1.00		
						Incremental net benefit per QALY	£730.12	£312.58	£908.49

Table 6.9: Results of the probabilistic sensitivity analysis combined for the mother and offspring and household (continued)

COMBINED MOTHER AND OFFSPRING: LIFETIME	**Mean**	**95% confidence interval**		**Mean**	**95% confidence interval**		**Mean**	**95% confidence interval**	
Expected cost	£35,471.20	£32,072.59	£40,559.66	£35,407.03	£31,994.34	£40,524.92	-£64.17	-£113.57	-£27.66
Expected Life Years	49.0868	48.9597	49.2049	49.1181	48.9914	49.2340	0.0313	0.0187	0.0489
Expected QALYs	44.0681	43.4028	44.6350	44.1059	43.4482	44.6672	0.0378	0.0229	0.0572
						Incremental cost per quitter	Dominant		
						Incremental cost per life year gained	Dominant		
						Incremental cost per QALY	Dominant		
						Probability cost-effective at £30,000 WTP	1.00		
						Incremental net benefit per QALY	£1,198.18	£739.16	£1,782.24
HOUSEHOLD: LIFETIME	**Mean**	**95% confidence interval**		**Mean**	**95% confidence interval**		**Mean**	**95% confidence interval**	
Number of quitters	53.68	46.62	60.75	88.28	77.92	98.48	34.60	29.27	40.32
Expected cost	£62,760.82	£58,574.77	£68,403.26	£62,548.17	£58,323.79	£68,229.34	-£212.65	-£287.50	-£156.88
Expected Life Years	73.7642	73.5884	73.9325	73.8048	73.6258	73.9722	0.0406	0.0271	0.0588
Expected QALYs	66.2728	65.2897	67.1039	66.3141	65.3227	67.1450	0.0413	0.0256	0.0607
						Incremental cost per quitter	Dominant		
						Incremental cost per life year gained	Dominant		
						Incremental cost per QALY	Dominant		
						Probability cost-effective at £30,000 WTP	1.00		
						Incremental net benefit per QALY	£1,450.87	£958.95	£2,063.02

Table 6.9: Results of the probabilistic sensitivity analysis combined for the mother and offspring and household (continued)

Healthcare savings return on investment (ROI)	**Mean**	**95%CI**	
At delivery	-1.59	-4.80	0.61
One year after delivery	0.09	-3.09	2.44
Mother and offspring lifetime	21.42	8.91	38.34
Household lifetime	70.91	49.37	100.96
Healthcare savings and QALY gains return on investment (ROI)	**Mean**	**95% CI**	
At delivery	11.79	7.17	17.74
One year after delivery	30.22	18.13	46.78
Mother and offspring lifetime	399.52	335.49	620.22
Household lifetime	483.76	305.41	708.76

The estimated incremental costs and QALY gains at delivery are displayed on the cost-effectiveness plane in Figure 6.2, one year after delivery in Figure 6.4, lifetime analysis for the mother and offspring in Figure 6.6 and for the household in Figure 6.8.

When only the pregnancy time horizon is considered, the cost per mother and infant increases (£5.79) along with the QALY gains (0.0013). Hence, the MiQuit intervention is cost-effective at a £30,000 WTP per additional QALY gained. Moreover, it is dominant in some of the iterations as shown in Figure 6.2.

According to the CEAC analysis, the probability of cost-effectiveness at delivery declines gradually if the WTP is lower than £10,000 as demonstrated in Figure 6.3.

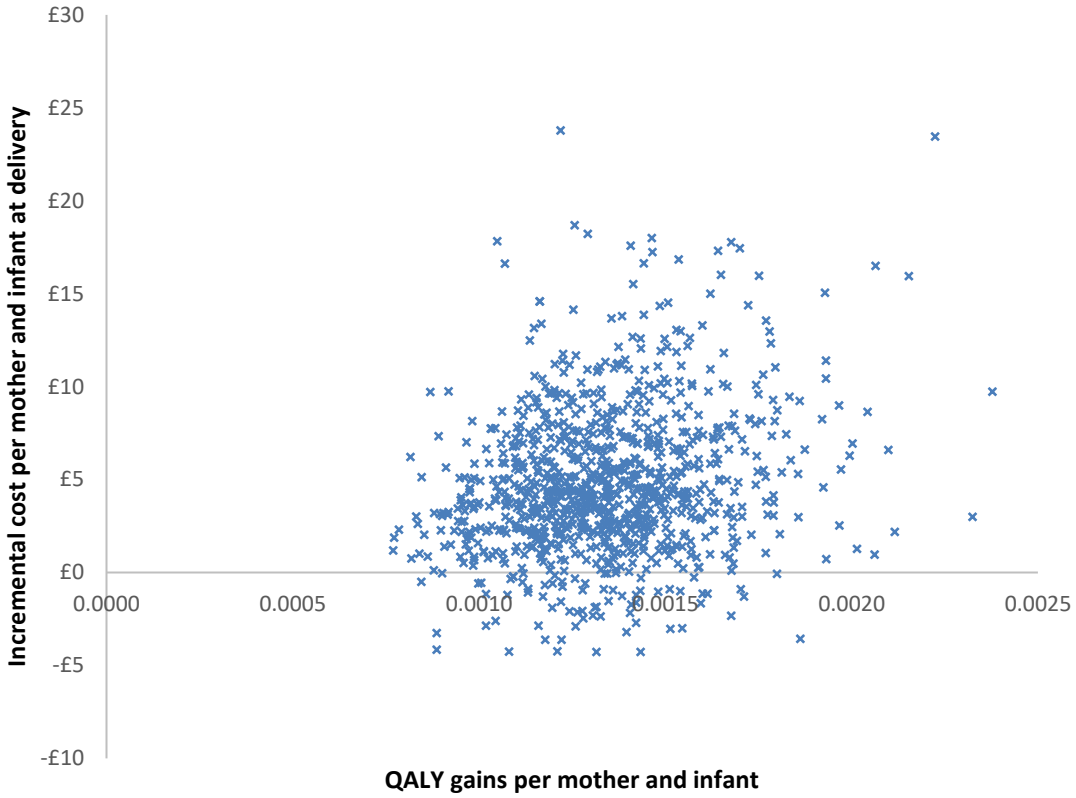


Figure 6.2: Scatterplot for incremental costs and QALY gains at delivery

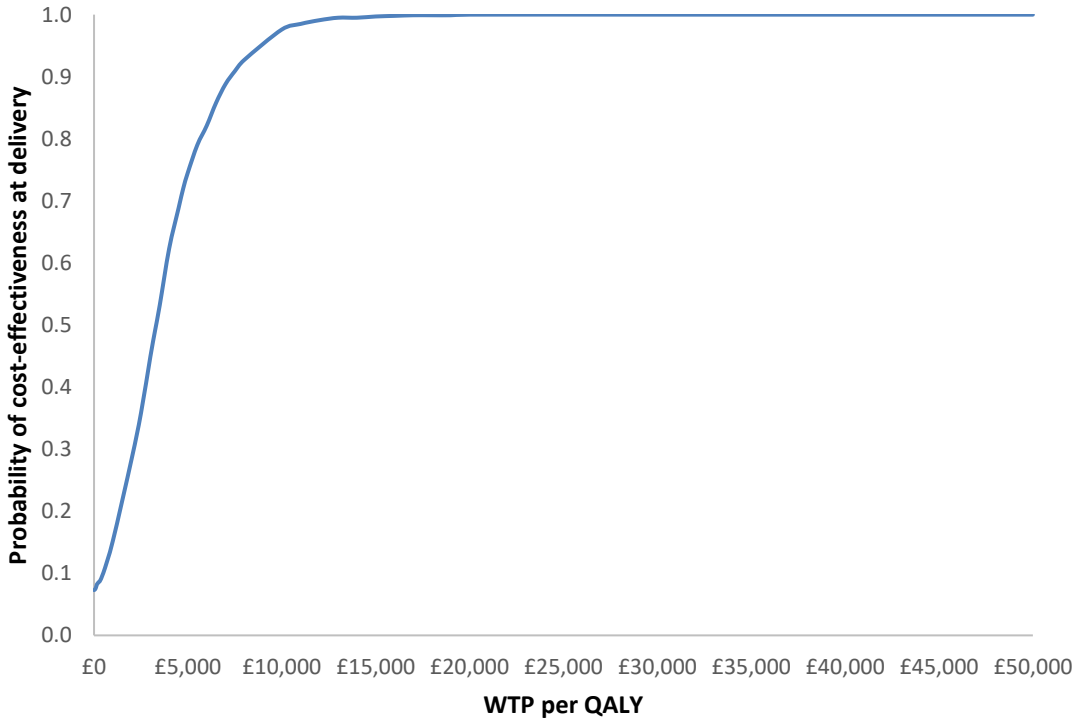


Figure 6.3: Cost-effectiveness acceptability curve for the mother and infant (at delivery)

At one year after delivery, the MiQuit intervention provides cost-savings (£0.26) and QALY gains (0.0030), and thus the intervention is dominant. However, there is some uncertainty around this estimation because around half the iterations fall in the northeast quadrant, meaning the intervention is not dominant but likely to be cost-effective.

The cost-effectiveness probability at one year after delivery reduces gradually for WTPs lower than £5,000 as shown in Figure 6.5.

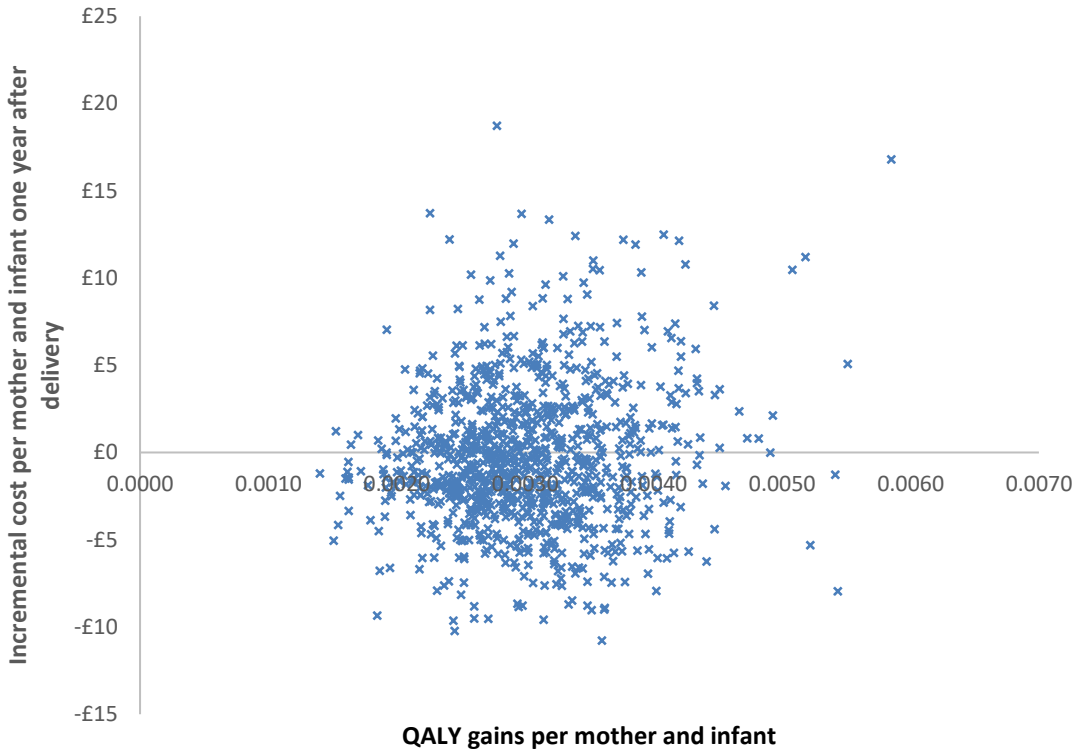


Figure 6.4: Scatterplot for the incremental cost per QALY per mother and offspring (one year after delivery)

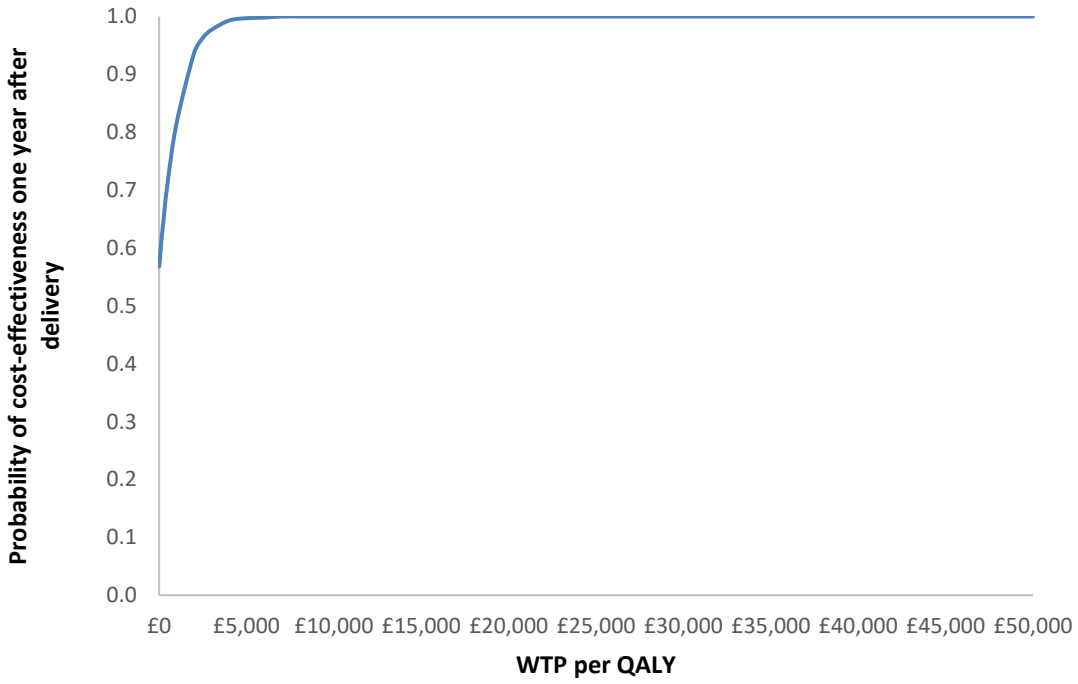


Figure 6.5: Cost-effectiveness acceptability curve for the mother and infant (one year after delivery)

In the both lifetime analyses, MiQuit provides significant cost-savings and QALY gains; hence it is dominant over the comparator. As seen in Figures 6.5 and 6.6, all iterations fall in the southeast quadrant, suggesting no uncertainty in the decision at a £30,000 per QALY threshold.

According to the CEACs, The MiQuit intervention is highly likely to be cost-effective at a £30,000 WTP per QALY in all time horizons. CEACs for the pregnancy period and one year after delivery analyses are demonstrated in Figures 6.3 and 6.5. The cost-effectiveness probability does not change for the lifetime horizon, and thus the graphs are not shown.

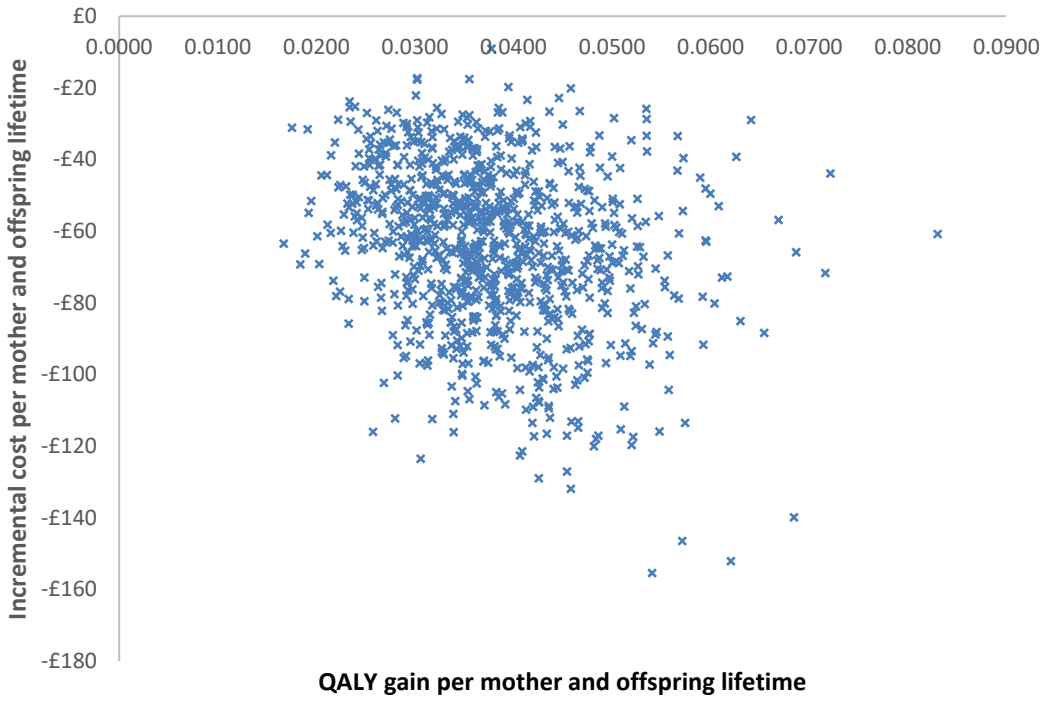


Figure 6.6: Scatterplot for the incremental cost per QALY per mother and offspring (lifetime)

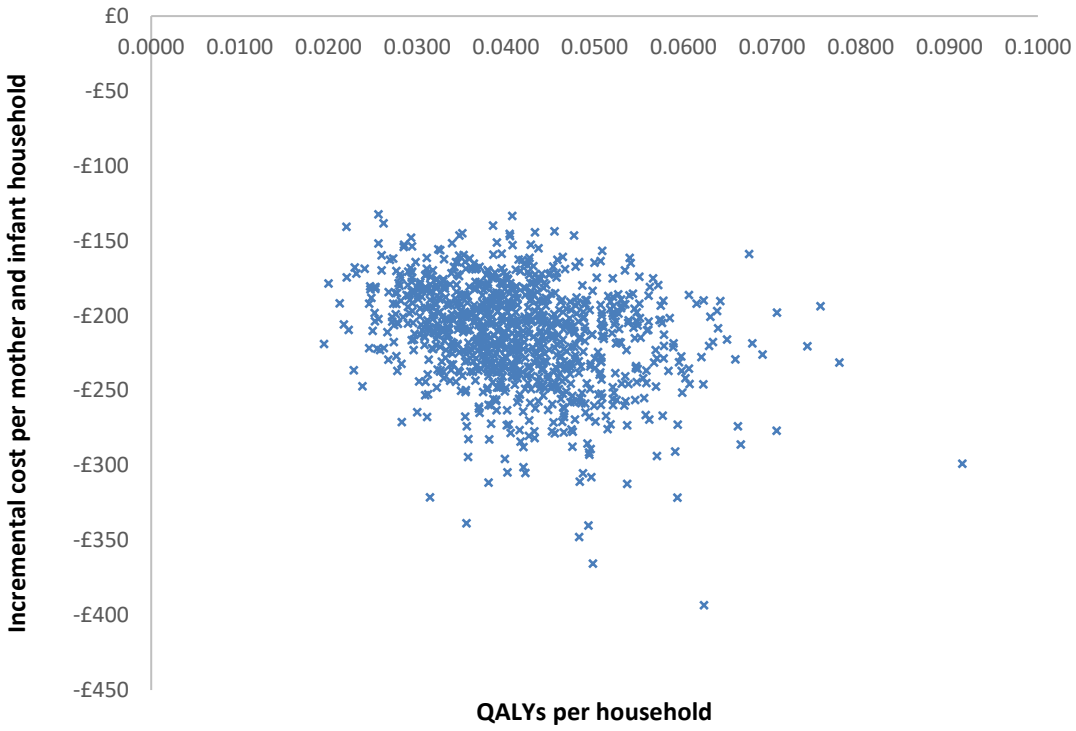


Figure 6.7: Scatterplot for the incremental cost per QALY per household

6.4.4 Expected Value of Perfect Information

As explained in section 5.2.6 an EVPI analysis was designed to estimate the value of additional information to reduce uncertainty at different WTP thresholds. According to that, the EVPI was zero at £30,000 in all analyses.

The PSA scatterplot for the within pregnancy analysis (Figure 6.2) shows virtual certainty that the intervention might be dominant not just cost-effective. On the other hand, the graph for one year after delivery (Figure 6.4) indicates some possibility that the intervention might be cost-effective not dominant. Therefore, if the decision-maker is interested in cost-effectiveness at a £30,000 per QALY threshold, further research would be of little benefit. Yet, if it is dominance that the decision-maker is looking for, further research should be considered for the one year after delivery analysis.

In the within pregnancy analysis and one year after delivery analysis, conducting further research warrants the highest value at £0 WTP per QALY when the maximum benefit per person is £4.91 and £1.40 respectively. The results are provided in Figures 6.8 and 6.9.

The PSA scatterplots for the lifetime analyses (Figures 6.6 and 6.7) show no uncertainty in the decision. That suggests additional information would not be of value at £30,000 threshold if the decision-maker is interested in the lifetime horizon. Since the EVPI was zero at all thresholds for the lifetime analyses, they are not shown.

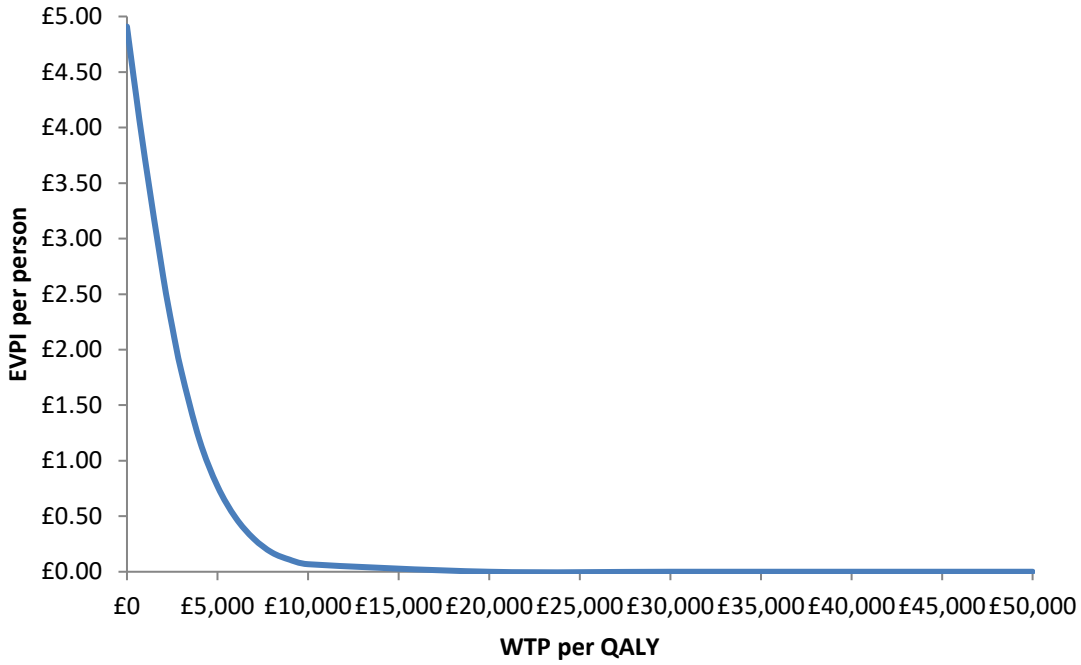


Figure 6.8: EVPI (within pregnancy analysis) for the MiQuit intervention

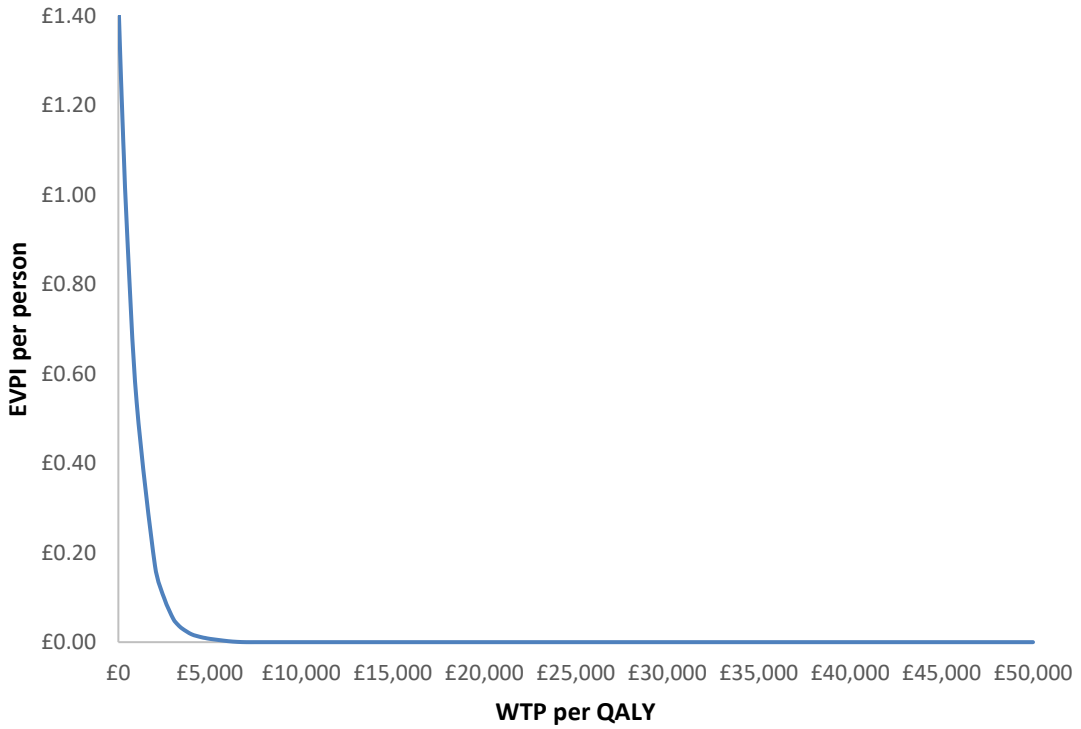


Figure 6.9: EVPI (one year after delivery analysis) for the MiQuit intervention

6.4.5 Comparing Findings of ESIP.H to ESIP

The overall findings of ESIP and ESIP.H are similar since MiQuit is a cost-effective intervention according to both models when only the pregnancy period is considered. Similarly, the intervention gains dominance in the lifetime analyses in both models. However, there are some differences in the models' findings. Table 6.10 below presents the incremental outputs in two models. Because ESIP did not estimate the outcomes at one year and from a household perspective, those outputs of ESIP.H are not provided in this section.

At the end of pregnancy, ESIP.H estimates a lower ICER compared to the figure in ESIP due to the greater estimated QALY gain in ESIP.H. The difference in QALY gains could be explained by the utility values estimated based on the severity of smoking in ESIP.H as opposed to a constant figure for all smokers in ESIP. Additionally, ESIP.H considers the impact of being a former smoker on ectopic pregnancy and miscarriage as well as the impact of severity of smoking on all pregnancy-related health conditions in contrast to ESIP. Linked to this, the different utility values used for smokers should be considered; for example, 0.23 utility loss (1.05 for never smokers) in ESIP against 0.27 in ESIP.H (0.987 for never smokers) amongst former smokers. ESIP.H also estimates a slightly higher cost per mother at delivery. That might be because of the difference in the number of deliveries since the cost of delivery is greater than the cost of ectopic pregnancy and miscarriage. Regarding the infant-related outcomes at delivery, ESIP.H estimates slightly greater cost per infant, which might be caused by slight increases in

health outcomes due to the impact of the partner's smoking and the severity of mother's smoking.

In the maternal lifetime analysis, ESIP.H estimates lower QALY gains and cost savings. This could be explained by the higher postpartum relapse rates applied in ESIP.H and the impact of including the severity of smoking and SHS on lifetime morbidities, which is not considered in ESIP. With respect to the offspring lifetime estimations, the two models estimate a similar improvement in health outcomes although ESIP.H includes SHS by mother's partner as well as by mother because ESIP.H used a greater SHS probability amongst offspring if parents smoke (80%) compared to ESIP (23%).

Despite the similar health outcomes in the offspring lifetime analysis, the cost savings are greater in ESIP.H (£50.79) than the figure in ESIP (£23.80). The difference might be caused by a number of factors. Firstly, incorporating partner smoking and maternal former smoking during pregnancy increases the stillbirth risk in ESIP.H, this is in contrast to ESIP which assumes the risk would be the same as for never smokers once a mother quits. A stillborn foetus does not acquire additional cost to the infant although it causes LYs and QALYs to be lost. An additional element might be the number of ever smokers in the adulthood components since ESIP does not consider the impact of the mother's partner in contrast to ESIP.H. That is important because smoking status affects the probability of death and quality of life. Using different utility values for smokers might be a significant contributor to the similar QALY gains in both models. Furthermore, due to a modelling error, the estimation by ESIP potentially does

not include the cost of death in the offspring adulthood component and hence the cost saving estimation does not include the savings accruing from prevented deaths.

Regarding the healthcare savings ROI estimations, according to both models the MiQuit intervention does not provide a positive return on the investment when only the pregnancy period is considered. In the lifetime horizon, however, it provides £21 for per £1 invested.

Table 6.10: Comparing the outputs of ESIP.H and ESIP

	Incremental outputs of ESIP			Incremental outputs of ESIP.H		
MATERNAL: END OF PREGNANCY	**Median**		**Interquartile range**	**Mean**	**95% confidence interval**	
Quit rate	3%	2%	5%	3%	3%	4%
Expected cost per mother	£4.71	£3.84	£5.91	£5.17	£3.23	£7.77
Expected QALYS per mother	0.0010	0.0006	0.0014	0.0013	0.0009	0.0019
Number of adverse pregnancy events	-1	-1	0	-1	-1	0
Incremental cost per quitter (mother)			**£153.96**			**£149.39**
Incremental cost per QALY (mother)			**£5,354.90**			**£3,864.28**
OFFSPRING: END OF PREGNANCY						
Number of foetuses lost	-1	-2	-1	-1	-2	-1
Number of preterm infants	0	-1	0	0	0	0
Number of LBW infants	-2	-3	-1	-2	-2	-1
Expected cost per infant	£1.74	-£0.76	£1.46	£2.47	-£3.51	£11.46
Incremental cost per QALY (mother and infant)			**£4,138.00**			**£3,582.68**
Return on Investment (mother and offspring healthcare only)	**-1.01**	**-1.80**	**-0.40**	**-1.59**	**-4.80**	**0.61**

Table 6.10: Comparing the outputs of ESIP.H and ESIP (continued)

	Incremental outputs of ESIP			Incremental outputs of ESIP.H		
MATERNAL: LIFETIME	**Median**	**Interquartile range**		**Mean**	**95% confidence interval**	
% cohort with morbidity at the age of 100	0%	0%	0%	0%	0%	0%
Expected LYs per mother	0.0028	0.0018	0.0041	0.0027	0.0017	0.0038
Expected QALYs per mother	0.0075	0.0046	0.0111	0.0067	0.0041	0.0102
Expected cost per mother	-£38.04	-£55.29	-£22.48	-£10.34	-£18.22	-£2.81
Incremental cost per QALY			**Dominant**			**Dominant**
OFFSPRING: LIFETIME						
% of ever smokers	0%	0%	0%	0%	0%	0%
Expected LYs per offspring	0.0290	0.0182	0.0413	0.0286	0.0166	0.0455
Expected QALYs per offspring	0.0311	0.0195	0.0444	0.0311	0.0178	0.0490
Expected cost per offspring	-£23.80	-£36.37	-£13.22	-£50.79	-£98.18	-£16.83
Incremental cost per QALY			**Dominant**			**Dominant**
COMBINED: MOTHER AND OFFSPRING LIFETIME						
Expected life years	0.0319	0.0201	0.0453	0.0313	0.0187	0.0489
Expected QALYs	0.0392	0.0244	0.0555	0.0378	0.0229	0.0572
Expected cost	-£60.70	-£89.00	-£35.45	-£64.17	-£113.57	-£27.66
Incremental cost per quitter at delivery (mother)			**Dominant**			**Dominant**
Incremental cost per QALY			**Dominant**			**Dominant**
Return on Investment (mother and offspring, healthcare only)	**21.06**	**12.64**	**30.58**	**21.42**	**8.91**	**38.34**

6.5 DISCUSSION

The analysis shows that MiQuit increases the number of quitters at delivery and one year after delivery and thus generates some health benefits. The economic evaluation finds MiQuit a cost-effective SDP intervention at within pregnancy analysis and dominant when the impacts beyond pregnancy are considered.

6.5.1 Strengths and Limitations

This study demonstrated the value of ESIP.H using an exemplar evaluation and showed its validity by comparing the outputs with the previous version of ESIP. However, the comparison was limited due to the constraints of the data collected for the MiQuit intervention. For example, partner smoking was only collected at registration and not at delivery. Hence, it was assumed that the proportion of smoking partners at delivery would be the same as the proportion at enrolment. Ideally the proportion of smoking partners at delivery should be entered the model. Yet, it was a reasonable assumption given that around 68% of pregnant women had smoking partners at delivery (Cooper et al. 2017, IFS, 2010).

Moreover, the proportion of smoking partners was assumed to be the same in the control and intervention groups although the study reported a lower figure in the control group at enrolment. This assumption was necessary to avoid underestimation of the benefits of MiQuit. The impact of this on the model outputs would be limited since the proportions at enrolment were similar in the control (63%) and intervention

groups (67%). However, this assumption also implies that MiQuit did not have any impact on partners' smoking which may or may not be true. The impact of this on the model results is not clear. If MiQuit did not affect partner smoking then the estimations would be accurate. On the other hand, if it increased the partner quit rates, the actual ICERs would be lower, suggesting the intervention is more cost-effective than shown in this study.

Although it was assumed that MiQuit had no impact on partners' smoking at delivery, ESIP.H was capable of estimating the spill-over impacts of MiQuit on partners in the lifetime analyses. With the increased the number of quitting mothers, the probability of quitting among smoking partners rose, and the mortality and morbidity risks among non-smoking partners due to SHS by mothers reduced.

Additionally, the MiQuit trial ended at delivery and no data was collected on the postpartum relapse rates. Thus, the model used the generic values reported in Table 5.21, which were significantly greater than the quit rates at delivery reported in the MiQuit study. As a result, the number of quitters one year after deliver was higher than those at delivery. Therefore, the model is potentially overestimating the number of quitters one year after delivery. Furthermore, the same postpartum quitting and relapsing probabilities were applied to the control and intervention groups. That was a reasonable assumption considering the intervention was short-term. However, if there was any decline in relapse rates in the intervention group or any increase in the quit rates one year after delivery, MiQuit would be more cost-effective than this study estimated.

6.5.2 Findings of ESIP.H in Comparison to ESIP

The overall findings of ESIP.H and ESIP for the MiQuit intervention are similar since both find the intervention cost-effective in the short-term and dominant in the lifetime analyses. The similar results in two models could be explained by the assumption that MiQuit have no effect on partner smoking at delivery and on postpartum relapse rates. However, for interventions with impacts on those, the outputs of two models would differ significantly.

In contrast to ESIP, ESIP.H incorporated the spill-over impacts of MiQuit on the mother's partner. To the best of the author's knowledge, this is the first economic evaluation to consider the spill-over effects of SDP interventions. Inclusion of the impacts on partner increased the incremental QALY gains from 0.0378 in the mother and offspring analysis to 0.0413 in the household analysis. Similarly, the expected cost savings increased from £64 to £213. Therefore, having a household perspective in economic evaluations of SDP interventions would provide more comprehensive evidence of economic benefit.

Despite similar cost-effectiveness results in the mother and offspring analyses, the model outputs differ in some important ways. At delivery, ESIP.H estimates a lower ICER for the MiQuit intervention, suggesting the intervention is more cost-effective than ESIP reports. That is caused by the inclusion of SHS by the partner, the severity of smoking and the impact of former smoking on ectopic pregnancy, miscarriage and stillbirth in ESIP.H. Similarly, according to the offspring lifetime and combined lifetime

analyses, the intervention is more cost-effective in ESIP.H than in ESIP, due to the greater SHS risk applied in ESIP.H compared to ESIP as well as incorporating the impact of the partner's smoking on smoking uptake by the offspring. This suggests that the previous evaluation of MiQuit with ESIP might be underestimating the benefits of the intervention.

On the other hand, in the maternal lifetime analysis, the cost-savings and QALY gains are lower in ESIP.H than in ESIP. Thus, when only the impacts on mother are considered, ESIP.H suggests that the MiQuit intervention is less cost-effective than what ESIP estimates. That is because of using considerably lower postpartum abstinence rate in ESIP.H (20%) compared to ESIP (53%). Since the figure used in ESIP.H is biologically verified, the outputs of ESIP.H would be more reliable than those of ESIP. Other factors explaining the difference between two model outcomes are including the impact of SHS and the severity of smoking since women living with smoking partners and heavy smokers are more likely to relapse to smoking. Overlooking those might cause overestimating the benefits of SDP interventions. Thus, ESIP.H provides more accurate results for decision-making by considering how partners' smoking affects mothers. The analysis also shows the need for future researchers to collect data on SHS, the severity of smoking and long-term quit rates during SDP interventions to be able to estimate the cost-effectiveness more precisely.

6.5.3 Policy Implications

The results show that adopting a household approach in economic evaluations of SDP interventions is important to estimate the benefits accurately. For example, the cost savings expected from the MiQuit intervention increased from £64 in the mother and offspring analysis to £213 in the household analysis. Thus, overlooking the spill-over effects might result in suboptimal policy decisions.

Similarly, considering the impacts beyond pregnancy affects the cost-effectiveness of SDP interventions. For example, the MiQuit intervention was cost-effective when only the pregnancy period is considered, while it was dominant over the comparator if the time horizon is extended to one year after delivery. Consideration of long-term outcomes was important regarding the ROI estimations as well since MiQuit could not pay the investment back at delivery or one year after delivery although it provided significant cost-savings in the lifetime analyses. Thus, decision-making based on the short-term ROI evidence might potentially result in sub-optimal decision-making.

Furthermore, the study found that significantly greater ROIs were generated when the spill-over impacts of SDP interventions on partner smoking were estimated. Hence, it is important to take those externalities into account.

6.6 CONCLUSION

MiQuit intervention is a cost-effective SDP intervention when only the pregnancy period is considered and it is dominant over the comparator if the outcomes one year

after delivery are also considered. When evaluating SDP interventions, having a household perspective is required to provide decision-makers with accurate estimations. However, it is also evident that the type of intervention represented by MiQuit has only very limited impact on helping women smoking while pregnant to quit, achieving only 3 additional quits one year after delivery amongst 1,000 mothers who are committed to quit.

6.7 CHAPTER SUMMARY

This chapter demonstrated the use and the validity of ESIP.H by evaluating MiQuit which is a low-cost text-based intervention aimed at pregnant smokers. The differences between the findings of ESIP.H and ESIP were also discussed. The study concluded that considering outcomes outside pregnancy and having a household perspective changed the cost-effectiveness results and the MiQuit intervention had a limited impact. The next chapter presents a study evaluating optimum SDP interventions, using ESIP.H.

CHAPTER 7: CHARACTERISTICS OF OPTIMUM SMOKING CESSATION INTERVENTIONS FOR PREGNANT WOMEN

7.1 INTRODUCTION

There is a need for novel SDP interventions to achieve greater and wider impact than the existing interventions have produced in order to achieve the national target of 6% or less SDP (Chapter 2). Therefore, this study aimed to evaluate the characteristics of optimum SDP interventions based on the available evidence, using the new economic model (ESIP.H) described in Chapter 5. This entailed modelling different intervention characteristics relating to alternating aims (from reducing smoking to achievement of a smoke-free household), content (e.g. behavioural intensity, and use of financial incentives) and duration (in response to high relapse rates).

The chapter starts with summarising the background information on novel SDP interventions that have been tested to date. Next, several hypothetical interventions that are designed based on the available evidence are evaluated.

7.1.1 Novel Interventions for Smoking Cessation during Pregnancy

The evidence suggests that the following features contribute to the most cost-effective SDP interventions: financial incentives with frequent contacts, lasting at least through to three months postpartum, and social supporters (e.g. partners) should be included where possible (Chamberlain et al., 2017, Morgan et al., 2015, WHO, 2013). To date, however, no trial combining intense long-term professional assistance, partner support and financial incentives has been published. In contrast, most SDP interventions have been low intensity, short-term and have focussed on women only (Chamberlain et al., 2017, Coleman et al., 2011).

Additionally, interventions have typically included women committed to quitting smoking, leaving those who were not yet ready to give up smoking without help (Chamberlain et al., 2017). However, assisting those women to reduce smoking would provide significant benefits since the health impacts of SDP are mostly dose-dependent (Burke et al., 2012, Conde-Agudelo et al., 1999, Marufu et al., 2015, Pineles et al., 2016, Shobeiri and Jenabi, 2017). Furthermore, as acknowledged in Chapter 5, individuals who smoke less than 10 cigarettes daily are more likely to quit than those who smoke more (Messer et al., 2008) and less likely to expose their children to SHS (see Section 5.2.4.3). Thus helping expectant mothers reduce SDP would increase their chances of quitting entirely and reduce maternal SHS amongst their children. The relevant evidence identified in the aforementioned review by Chamberlain et al. (2017) is summarised in Table 7.1.

Table 7.1: Quit and reduction rates in selected studies

	Intervention	Control	Increase	CO verified	Source
Quit rates amongst women around delivery					
Financial incentives	23%	9%	14%	YES	Tappin et al. (2015)
Partner support	42%	38%	4%	NO	McBride et al. (2004)
Financial incentives and social support	32%	9%	23%	YES	Donatelle et al. (2000)
Significant reduction in smoking amongst women around delivery					
Smoke-free house (>50% reduction)	11%	7%	4%	YES	Windsor et al. (2014)
Financial incentives (75% reduction in CO levels)	48%	0	48%	YES	Tuten et al. (2012)
Probability of long-term abstinence amongst women who quit during pregnancy					
Financial incentives (6 months after quitting)*	35%	19%	16%	YES	Tappin et al. (2015)
Partner support (12 months postpartum)	48%	40%	8%	NO	McBride et al. (2004)
Abstinence rates among partners					
Two months after delivery	17%	11%	6%	NO	McBride et al. (2004)
Abstinence among quitters (12 months)	73%	71%	2%		

***Estimated by dividing the number of abstinent women at follow-up by the number of those quit at delivery.**

7.2 METHODS

7.2.1 Characteristics of Optimum SDP Interventions

Based on the above outlined evidence showing the impact of financial incentives in combination with social support and the significance of partners, two exemplar cessation interventions called “Smoke-free house until 3 months postpartum (SFH3m)” and “Smoke-free house until 12 months postpartum (SFH12m)” and one exemplar reduction intervention called “Reduced smoking during pregnancy (RSDP)” were

designed. The characteristics of these hypothetical interventions are summarised in Table 7.2.

Table 7.2: Characteristics of the hypothetical interventions

Characteristics	Control	SFH3m	SFH12m	RSDP
Duration	4 weeks	3 months postpartum	12 months postpartum	delivery
Face-to-face contacts	1	19	29	16
Phone contact	4	1	0	1
Self-help materials	Yes	Yes	Yes	Yes
NRT	10 weeks	10 weeks	10 weeks	10 weeks
Partner included	No	Yes	Yes	No
Vouchers per household	0	Up to £1,520 £40 for woman and partner if CO specimen is negative (Non-smoking partner,£40 contingent on woman's negative CO specimen)	Up to £2,320 Same as SFH3m	Up to £640 £40 for woman only contingent on >50% reduction CO levels
Outcome	Abstinence	Abstinence	Abstinence	>50% reduction

7.2.1.1 Control group

The control group was defined based on the available evidence on the standard support provided for pregnant smokers in the UK (see Section 2.3.2). Every pregnant smoker is offered one face-to-face contact in a maternity care setting that is followed by 10 weeks NRT, self-help materials and four weekly phone calls (Table 7.2). Although NRT has very limited impact on quit rates and only a limited proportion of pregnant women who would like to quit use NRTs, it was incorporated in the control and intervention arms since it is the standard practice (Cooper et al. 2014b, Ussher et al. 2015).

7.2.1.2 Smoke-free house until 3 months postpartum (SFH3m)

The first hypothetical intervention, SFH3m, was designed based on an optimum SDP intervention described by the NIHR-funded study by Morgan et al. (2015), which drew on a discrete choice experiment and several systematic reviews. The study found that an optimum intervention should include the following; frequent regular contacts with healthcare professionals, lasting up to three months postpartum, financial vouchers of up to £80 per month contingent on CO monitoring of cessation, and a supporting buddy.

In England, half the pregnant women had their first pregnancy related contact with a health professional at between 7th and 12th weeks of gestation while the other half had it by six weeks (Care Quality Commission, 2018). Thus, it would be reasonable to assume that the first appointment would take place at around the seventh week, suggesting maximum of 18 midwife visits in addition to the initial session. Women would also receive a follow-up phone call one year after delivery to obtain their smoking status.

The evidence suggested that the most critical times regarding re-starting smoking were the first four weeks following a quit attempt and around delivery (Jones et al., 2016, Morgan et al., 2015). Therefore, it was appropriate that midwife visits would take place every week during the first four weeks after the enrolment and during the four weeks just before and after delivery, with monthly visits in between.

It was assumed that every participant would be offered £40 for an initial face-to-face contact in maternity care setting, as in the trial by Tappin et al. (2015). During the initial meeting, a quit date would be set with participants. Women and partners would receive counselling and cessation aid during pregnancy and until three months postpartum. Although NRT has very limited impact on quit rates and only a limited proportion of pregnant women who would like to quit use NRTs, it was incorporated in the control and intervention arms since it represents standard practice (Cooper et al. 2014b, Ussher et al. 2015).

The SFH3m intervention would include offering 10 weeks of NRT, self-help materials and midwife visits, and £40 vouchers per negative CO specimen (on average £80 monthly). Non-smoking partners could earn vouchers contingent on the women's abstinence. Additionally, women with no partners could include a significant other. Therefore, overall one couple could receive up to £1,520.

7.2.1.3 Smoke-free house until 12 months postpartum (SFH12m)

The second hypothetical intervention was designed in response to the high relapse rates after delivery (Jones et al., 2016). Women and partners would receive the above identified support until three months postpartum (up to £2,230) and monthly midwife visits between three and 12 months postpartum.

7.2.1.4 Reduced smoking during pregnancy (RSDP)

The third hypothetical intervention was designed for expectant mothers who were not ready to quit entirely, assisting them in reducing smoking. In this intervention, women would be provided counselling and cessation aid during pregnancy until delivery. This would include offering 10 weeks NRT, self-help materials and midwife visits as described in SFH3m. Women would be provided £40 voucher each per CO specimen showing they had cut their smoking by half compared to the start of the intervention.

7.2.2 Effectiveness

The effectiveness of the comparator and interventions in this study were estimated based on the data from the trials which included women who wanted to quit smoking (Table 7.1). The evidence outlined in Table 7.1 indicates that including partners resulted in a 4% point increase in quit rates amongst expectant mothers and the figure was 23% when a social supporter and low level of incentives were incorporated (Donatelle et al., 2000, McBride et al., 2004). Similarly, postpartum abstinence amongst women increased by 8% when partners were included and 16% when they were offered up to £400 vouchers (McBride et al., 2004, Tappin et al., 2015).

Additionally, the higher the level of incentives the greater the impact would be, since a meta-analysis of interventions targeting substance use (Lussier et al., 2006), including smoking, estimated that providing $5 daily (in 2006 prices) would increase abstinence by 23%, and above $16 by 43%. Similarly, the trial by Tappin et al. (2015) provided £60 vouchers per month (max. £400 per woman) and achieved a 22.5% quit rate at

delivery. Boyd et al. (2016) assumed that an intervention offering up to £1,800 per pregnant smoker would increase effectiveness from 23% to 43%.

Moreover, evidence showed that increased contacts at early stages promoted behaviour change in smokers (Free et al., 2011) and longer support reduced relapse rates (Helgason et al., 2009).

7.2.2.1 Control group

Regarding quit and abstinence probabilities amongst expectant mothers, the mean quit rate of 9% at delivery estimated by Jones (2015) based on SDP trials was deemed appropriate for the control group because the aim of the analysis was to evaluate the cost and health impacts of such interventions on women seeking help. With respect to partner behaviour, the figures reported in Section 5.2.3.2 were also utilised; it was assumed that approximately 3% of smoking partners quit at delivery. Similarly, the abstinence probability one year after delivery (20%) (Ratner et al., 1999) was applied for both mothers and partners due to the absence of bio-chemically verified data for partners (see Section 5.2.1.2.1).

7.2.2.2 Interventions

7.2.2.2.1 Hypothetical cessation interventions (SFH3m and SFH12m)

Since there was no published trial with the characteristics outlined in this study, the effectiveness of hypothetical interventions was determined from the author's estimates of the combined impact of the interventions' components based as far as

possible on the outcomes of existing trials (Table 7.1). Hence, the 'base-case' scenario is compared to a 'cautious-case' scenario, which takes a pessimistic view on expected outcomes (SFH3m and SFH12m).

In the base-case scenario, the quit rate among women at delivery for the SFH3m intervention was estimated as 43% (Lussier et al., 2006) assuming that SFH3m would have a greater impact than the trial by Tappin et al. (2015) because women were offered higher level of incentives and significantly more contacts (6 vs. 20) in addition to including partners. Abstinence at 12 month for SFH3m (16% increase) was taken from the incentives alone trial (Tappin et al. 2015) and the impact of partner support (McBride et al. 2004) was added (16%+8%=24%) to obtain the rate for the SFH12m trial.

The expected effectiveness of the designed cessation interventions (SFH3m and SFH12m) in the 'base-case' and 'cautious-case' scenarios were estimated as shown in Table 7.3.

Table 7.3: Estimated effectiveness of the hypothetical cessation interventions

	Outcomes			**Control (%)**	**Source**
Control	Quit rate at delivery	women		9	Jones (2015)
		partners		3	
	12 month abstinence among quitters	women		20	Ratner et al. (1999)
		partners		20	
Scenarios	**Outcomes**		**SFH3m (%)**	**SFH12m (%)**	**Based on author's estimates and the following sources***
Base-case	Quit rate at delivery	women	43	43	Tappin et al. (2015), Boyd et al. (2016).
		partners	15	15	McBride et al. (2004)
	12 month abstinence among quitters	women	36	44	Tappin et al. (2015), McBride et al. (2004).
		partners	24	28	McBride et al. (2004), Nohlert et al. (2009).
Cautious-case	Quit rate at delivery	women	32	32	Donatelle et al. (2000)
		partners	9	9	McBride et al. (2004)
	12 month abstinence among quitters	women	28	36	McBride et al. (2004)
		partners	22	24	McBride et al. (2004)

***The assumptions made about those are explained in the text.

In the cautious-case scenario, SFH3m and SFH12m were estimated to have the same impact on mothers at delivery as the financial incentives and social support (23% increase) (Donatelle et al. 2000). Similarly, the probability of abstinence for SFH3m were taken from the partner support study (8% increase, McBride, 2004). It was assumed that in SFH12m the effect would be doubled (16% increase) based on the evidence showing the impact of longer-term support (Nohlert et al., 2009).

Regarding the quitting probabilities among partners, they were assumed to be twice the intervention by McBride et al. (2004) (12% and 4%) in the base-case scenario, whereas in the cautious-case, the increase in quit (6%) and abstinence rates (2%)

would remain the same as in the intervention by McBride et al. (2004). For SFH12m, the abstinence rates were twice those for SFH3m.

The quit and abstinence rates (Table 7.2) were adjusted based on partner smoking by applying the methods explained in Chapter 5. The estimated figures are presented in Table 7.4:

Table 7.4: Estimated effectiveness of the hypothetical cessation interventions based on SHS exposure

Outcomes			**Partner smokes**		**Partner does not smoke**	
			Control (%)		**Control (%)**	
Control	Quit rate at delivery	women	6		14	
		partners	3		NA	
	12-month abstinence among quitters	women	3		46	
		partners	3		46	
Scenarios	**Outcomes**		**SFH3m (%)**	**SFH12m (%)**	**SFH3m (%)**	**SFH12m (%)**
Base-case	Quit rate at delivery	women	34	34	55	55
		partners	15	15	NA	NA
	12-month abstinence among quitters	women	19	27	62	84
		partners	7	11	50	54
Cautious-case	Quit rate at delivery	women	24	24	43	43
		partners	9	9	NA	NA
	12-month abstinence among quitters	women	11	19	54	62
		partners	5	7	48	50

7.2.2.2.2 Reduction intervention (RSDP)

Similar assumptions were made to estimate the expected effectiveness of RSDP intervention (Table 7.5). According to the trial by Cooper et al. (2017) the proportions of light, moderate and heavy smokers among pregnant smokers were 0.4, 0.32, and 0.28 respectively, which were used for the comparator. Since there was no evidence on the impact of financial incentives amongst women who did not want to quit but

wanted to reduce, the evidence from the trial which included women who set a quit date was utilised (Tuten et al. 2012).

Table 7.5: Effectiveness of the hypothetical reduction intervention (RSDP)

Scenarios	Outcomes	Of smokers	Based on
Comparator	Light smokers	0.40	Cooper et al. 2017
	Moderate smokers	0.32	
	Heavy smokers	0.28	
Base-case	Light smokers	0.81	Tuten et al. 2012, Lussier et al. 2006
	Moderate smokers	0.10	
	Heavy smokers	0.09	
Cautious-case	Light smokers	0.69	Tuten et al. 2012
	Moderate smokers	0.17	
	Heavy smokers	0.14	

Tuten et al. (2012) reported a 48% increase in the number of women who reduced smoking when they were provided with up to $42 vouchers. In the base-case scenario, the increase rate was calculated as 69% based on the ratio (43% increase) reported by Lussier et al. (2009). Reduction in smoking would not change the group of light smokers because they would be considered as light smokers even if they smoke only one per day. Thus, the proportions in the base-case would be 0.81, 0.11 and 0.09. In the cautious-case scenario, the increase rate (48%) reported by Tuten et al. (2012) was applied, hence the proportions would be 0.69, 0.19 and 0.15 respectively.

In the absence of data showing the relationship between reducing smoking during pregnancy and partner smoking, it was assumed that it did not have any impact on the probability of reducing daily cigarette consumption. Additionally, to enable comparability with the cessation interventions, a 9% quit rate which was estimated based on the trials that included women who wanted to quit was also applied for women receiving the RSDP intervention as well as those in the control group.

7.2.3 Costs

The unit costs used for calculating the sum cost of hypothetical interventions are provided in Table 7.6. The training cost per counselling session by a midwife in a hospital setting was obtained from the SNAP trial (Cooper et al. 2014b), estimated based on the provision of two-day training for 10 midwives (midpoint salary band 7) by a NHS SSS advisor (an average of salary bands 5 and 6). This training cost was applied as a one-off cost per mother. The remainder were obtained from the relevant national dataset or the SNAP trial and inflated to 2014-2015 prices where necessary (Cooper et al., 2014b).

Table 7.6: Unit costs for the hypothetical interventions

Cost area	Unit cost (2014/15)	Source
Training midwives	£4.81*	SNAP trial
First counselling session	£38.50*	SNAP trial
Antenatal community midwife visit	£55.51	NHS Reference Costs (2014-2015)
Postnatal community midwife visit	£69.55	NHS Reference Costs (2014-2015)
NRT	£9.37	BNF 2018
CO monitor	£0.51*	SNAP trial
Printing	£1.11*	SNAP trial
Phone call (4 minutes)	£1.39*	SNAP trial
Voucher per specimen	£40	Based on the study by Boyd et al. (2015)
Initial voucher	£40	Based on the study by Tappin et al. (2015)
Postage costs for vouchers	£1.8	Royal mail signed first class delivery price (Royal Mail, 2014)

*Inflated to 2014-2015 prices based on national inflation indices (Curtis and Burns, 2018)

7.2.3.1 Cost of vouchers

Since the greatest cost component was the vouchers, specific attention was paid to produce a robust estimate for the voucher costs. The actual cost would be much lower than the maximum available vouchers because of participants not achieving the quit status criteria and subsequent relapses. For instance, in the study by Tappin et al. (2015), the maximum available vouchers summed up to £400 while the actual mean cost was £127.

To estimate the cost of vouchers for the cessation interventions (SFH3m and SFH12m), abstinence amongst mothers at different time points was estimated based on the control group results of the studies reported in the systematic review by Jones et al. (2016), which measured biochemically verified continuous abstinence. According to this review, abstinence rates were as follows; 0.54 eight weeks post-randomisation, 0.44 three months after delivery and 0.26 six months after delivery. Additionally, as discussed in Chapter 5, one year abstinence amongst those who quit at delivery to be 0.20 (Ratner et al., 1999). The abstinence levels for the hypothetical cessation interventions were calculated based on the probabilities in Table 7.4.

Riaz et al. (2018) reported that women who had a smoking partner were less likely to quit during pregnancy (OR= 0.42, 95% CI, 0.35-0.50) and Ratner et al. (2000) estimated that women with a smoking partner were more likely to relapse one year after delivery (RR=1.81, 95% CI, 1.02-3.2). Thus, the quit and abstinence probabilities were adjusted according to whether there was a partner who smoked, applying the same methods

outlined in Section 5.2.1.2.1. The abstinence probabilities amongst all trial participants used in the voucher cost estimations are presented in Table 7.7.

Table 7.7: Abstinence levels amongst mothers at different time points used for voucher cost calculations

	Control		SFH3m-base		SFH3m-cautious		SFH12m-base		SFH12m-cautious	
Partner smokes	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
8 weeks post-randomisation	0.07	0.17	0.41	0.67	0.29	0.52	0.41	0.67	0.29	0.52
Delivery	0.06	0.14	0.34	0.55	0.24	0.43	0.34	0.55	0.24	0.43
3 months postpartum	0.02	0.09	0.16	0.43	0.10	0.31	0.16	0.43	0.10	0.31
6 months postpartum	0.00	0.07	0.08	0.36	0.04	0.25	0.11	0.40	0.08	0.28
12 months postpartum	0.00	0.06	0.06	0.34	0.03	0.23	0.09	0.39	0.06	0.27

The abstinence rates among partners were estimated based on the effectiveness estimations above (Table 7.3) and the transition probabilities calculated based on mothers' abstinence levels, assuming they would be the same among partners due to a lack of data. In the absence of data showing the impact of a pregnant woman's smoking on partner's smoking behaviour, it was assumed that quit rates amongst partners were not affected by women's smoking. However, since the relapse rates at one year amongst partners were assumed to be the same as women's (0.03 in SHS exposed and 0.46 in SHS unexposed), the same was applied for relapse rates at three months and six months as well. Table 7.8 below shows the abstinence levels amongst smoking partners. Since non-smoking partners received vouchers contingent on women's abstinence, no such estimation was required for them.

Table 7.8: Abstinence levels amongst partners at different time points used for voucher cost estimations

	Control		SFH3m base		SFH3m cautious		SFH12m base		SFH12m cautious	
Partner smokes	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
8 weeks post-randomisation	0.07	0.17	0.17	0.17	0.11	0.11	0.17	0.17	0.11	0.11
Delivery	0.06	0.14	0.14	0.14	0.09	0.09	0.14	0.14	0.09	0.09
3 months postpartum	0.02	0.09	0.06	0.10	0.03	0.06	0.06	0.11	0.03	0.06
6 months postpartum	0.00	0.07	0.02	0.08	0.01	0.05	0.02	0.09	0.02	0.08
12 months postpartum	0.00	0.06	0.01	0.08	0.00	0.05	0.02	0.08	0.01	0.08

The cost of vouchers including postage per person was estimated based on the total number of visits and abstinence rates (Tables 7.7 and 7.8). Table 7.9 presents the voucher cost estimations.

Table 7.9: Voucher costs estimated based on abstinence at different time points

	N Visit	SFH3m base		SFH3m cautious		SFH12m base		SFH12m cautious	
Partner smokes		**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
8 weeks post-randomisation	8	£269.54	£525.70	£213.43	£428.46	£269.54	£525.70	£213.43	£428.46
Around delivery	8	£165.19	£367.84	£111.69	£287.58	£165.19	£367.84	£111.69	£287.58
3 months postpartum	2	£18.93	£72.65	£10.93	£51.05	£19.44	£72.65	£10.93	£51.05
6 months postpartum	3	0	0	0	0	£17.59	£100.70	£13.20	£70.10
12 months postpartum	7	0	0	0	0	£33.60	£225.30	£22.23	£159.04
TOTAL		**£453.66**	**£966.19**	**£366.05**	**£767.09**	**£505.37**	**£1,292.19**	**£371.42**	**£996.22**

The voucher costs for the reduction intervention (RSDP) were calculated based on their expected impact at delivery since no study was identified that reported a reduction in smoking at different time points before delivery. Hence, in the base-case scenario, 69% of expectant mothers received vouchers and 48% in the base-case, incurring £441.60 and £307.20 in voucher costs, respectively.

7.2.3.2 Intervention costs

The expected costs for the hypothetical interventions are presented in Table 7.10. Assumptions for the cost estimations were as follows.

1. It was assumed that NRT, self-help materials, one counselling session and four phone calls were provided in the control group.
2. Participants in the intervention groups received a £40 voucher for attending the first session based on the trials by Tappin et al. (2015) and Tuten et al. (2012).
3. All women were assumed to have partners. That is because women who did not have partners would be able to bring any smoking household member or if the woman is the only smoker at home they can assign a significant other (non-smoker) to support them.
4. Although the uptake of NRT is very low, it was assumed that every participant would take the 10-week NRT support.
5. 68% of women had smoking partners and non-smoking partners were eligible for vouchers contingent on women's abstinence. However, they would not need NRT treatment and that was taken into account in cost estimations.
6. The abstinence rates and the intervention costs in trials were estimated based on the data from trials showing that abstinence would diminish in time. It was assumed that women who were lost to follow-up relapsed to smoking. Hence, no additional estimate was conducted for that.

Table 7.10: Estimated cost of the hypothetical interventions

Base scenario	**Control**	**SFH3m**		**SFH12m**		**RSDP**	
Partner smokes	**Either**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Initial appointment (incl. training)+ NRT+ leaflet per couple	£133.31	£227.01	£133.31	£227.01	£133.31	£133.31	£133.31
Midwife visit+ CO monitors	0	£384.32	£667.81	£452.34	£941.01	£618.46	£618.46
Phone calls	£5.51	£1.39	£1.39	0	0	0	0
Vouchers	0	£453.66	£966.19	£505.37	£1,292.19	£441.60	£441.60
Total per household	**£138.87**	**£1,066.38**	**£1,768.70**	**£1,186.11**	**£2,367.90**	**£1,193.37**	**£1,193.37**
Cautious scenario	**Control**	**SFH3m**		**SFH12m**		**RSDP**	
Partner smokes	**Either**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Initial appointment (incl. training)+ NRT+ leaflet per couple	£133.31	£227.01	£133.31	£227.01	£133.31	£133.31	£133.31
Midwife visit+ CO monitors	0	£268.88	£517.28	£315.98	£709.31	£430.23	£430.23
Phone calls	£5.51	£1.39	£1.39	0	0	0	0
Vouchers	0	£354.37	£870.18	£399.83	£1,019.31	£307.20	£307.20
Total per household	**£138.87**	**£833.33**	**£1,419.07**	**£915.86**	**£1,840.23**	**£870.74**	**£870.74**

For example, the cost of each visit around delivery for those unexposed to SHS in the base-case scenario was calculated as follows:

$$(\text{Cost (Postnatal midwife visit)} + \text{Cost (CO monitor)} + \text{Cost (vouchers per couple)}) * \% \text{ (abstinent around delivery)}$$

= (£69.55+£0.51+£40*2)*0.55 =£84.53

In the absence of data, the proportions of women who reduced smoking by 50% and hence were entitled to vouchers were assumed to be the same throughout the RSDP intervention.

7.3 ANALYSIS

The 'base-case' and 'cautious-case' scenario analyses were conducted for evaluating the hypothetical interventions. The decision analytic model, ESIP.H, described in Chapter 4 was used to estimate the cost-effectiveness of the hypothetical interventions and to conduct ROI analyses. The analyses were conducted from an NHS perspective. The model used annual cycles and future costs and benefits were discounted at 3.5%.

The model outputs were listed in Section 5.2.6, including number of quitters for the cessation interventions and number of reducers for the reduction intervention, ICERs at delivery, one year after delivery and over the life-time horizon. The ROI analyses included two calculations; one covering the NHS healthcare cost savings only (ROI1) and the second capturing health gains as well (RO2), by assigning a monetary value of £30,000 per QALY gain. Probabilistic sensitivity analysis (PSA) was conducted to analyse the uncertainties around the model findings, following the methods described in section 5.2.7.2.

7.4 RESULTS

7.4.1 Deterministic Results

In the within pregnancy analysis, SFH3m and SFH12m generate 351 additional quitters amongst the mothers in the base-case while this figure is 230 in the cautious-case.

When partners are also included the numbers rise to 467 and 286, respectively. The incremental cost per QALY (ICER) estimated for SFH3m is £94,999 in the base-case and £119,984 the cautious-case scenario, which are significantly greater than the NICE threshold of £30,000. Similarly, the ICER estimates for SFH12m are £125,960 in the base-case and £152,187 in the cautious-case scenario. Thus, the interventions would not be considered cost-effective if the decision-maker is interested in the pregnancy period only.

One year after delivery in the base-case scenario, 127 women in SFH3m and 162 women in SFH12m are abstinent in addition to 140 in the control. Those figures are 58 in SFH3m and 109 in SFH12m according to the cautious-case estimates. That output includes the number of women who quit at delivery and remained abstinent as well as those who quit one year after delivery despite smoking during pregnancy. Since the number of women who continue smoking during pregnancy is significantly higher in the control group than in SFH3m and SFH12m, the number of new quitters is greater in the control than in the intervention groups. Similarly, since the number of quitters is lower in the control than in the interventions, the number of women who relapse to smoking is higher in the interventions than in the control. As a result, the sum of women who are abstinent one year after delivery is greater than the number of quitters in the control, whereas the opposite is the case in the interventions.

Although the ICERs in the one year after delivery analyses are less than half of those in the within pregnancy analyses for both SFH3m and SFH12m interventions, they still remain relatively high compared to the NICE threshold (Tables 7.11 and 7.12). the

interventions are cost-effective when the impacts on the offspring in childhood are included. Although the interventions do not reduce SID, they generate more QALYs because of avoided childhood morbidity (asthma and LRI).

In the mother and offspring lifetime analyses, both cessation interventions are cost-effective. The ICER estimated for SFH3m is £1,224 in the base-case scenario and £2,230 in the cautious-case. The ICERs for SFH12m are £1,914 in the base-case and £2,671 in the cautious-case (Tables 7.11 and 7.12).

Table 7.11: Deterministic outcomes of the hypothetical interventions (Base-case)

	Control	SFH3m Base-case		SFH12m Base-case		RSDP Base-case	
End of pregnancy		**Experimental**	**Incremental**	**Experimental**	**Incremental**	**Experimental**	**Incremental**
Number of quitters/reducers (mother only)	88.00	438.70	350.70	438.70	350.70	697.06	697.06
Number of foetuses lost	102.23	92.04	-10.18	92.04	-10.18	90.78	-11.45
Number of infants born prematurely	69.05	66.36	-2.69	66.36	-2.69	69.12	0.06
Number of infants born with LBW	99.47	83.97	-15.50	83.97	-15.50	91.47	-8.01
Expected QALYs per mother	0.6348	0.6483	0.0134	0.6483	0.0134	0.6473	0.0125
Expected cost per mother and infant	£7,193.65	£8,470.02	£1,276.36	£8,886.01	£1,692.35	£8,316.66	£1,123.01
Incremental cost per QALY			£94,998.57		£125,960.17		£89,871.00
End of one year after delivery							
Number of quitters (mother only)	139.96	267.28	127.32	302.36	162.40	178.35	38.39
Expected LYs per mother and infant	2.5376	2.5536	0.0159	2.5536	0.0159	2.5550	0.0174
Expected QALYs per mother and infant	2.3439	2.3772	0.0333	2.3783	0.0343	2.3791	0.0352
Expected cost per mother and infant	£7,602.73	£8,824.20	£1,221.47	£9,238.09	£1,635.36	£8,687.79	£1,085.05
Incremental cost per QALY			£36,732.53		£47,669.75		£30,852.78
Offspring age 15 (end of childhood)							
Number of SID	1.42	1.28	-0.14	1.28	-0.14	1.27	-0.15
Expected LYs per child	10.2800	10.4037	0.1237	10.4037	0.1237	10.4142	0.1342
Expected QALYs per child	10.0483	10.2011	0.1528	10.2016	0.1533	10.2068	0.1585
Expected cost per child	£7,283.86	£8,053.10	£769.24	£8,460.63	£1,176.77	£7,969.68	£685.82
Incremental cost per additional QALY			£5,034.07		£7,675.20		£4,326.49
Mother and offspring lifetime combined							
Expected life years	49.2080	49.5509	0.3429	49.5602	0.3522	49.5388	0.3308
Expected QALYs	44.0641	44.4903	0.4262	44.5109	0.4468	44.4569	0.3928
Expected cost	£36,136.47	£36,657.94	£521.47	£36,991.50	£855.03	£36,898.72	£762.25
Cost per quitter/reducer at delivery (mother only)			£1,486.94		£2,438.05		£1,042.78
Incremental cost per QALY			£1,223.51		£1,913.76		£1,940.76
Mother, partner and offspring lifetime combined							
Number of quitters/reducers at delivery (mother and partner)	122.00	588.70	466.70	588.70	466.70	697.06	697.06
Expected life years	73.9208	74.3571	0.4363	74.3677	0.4470	74.2516	0.3308
Expected QALYs	66.3108	66.7817	0.4709	66.8045	0.4936	66.7036	0.3928
Expected cost	£63,099.30	£62,105.89	-£993.41	£62,424.28	-£675.03	£63,861.55	£762.25
Cost per quitter/reducer (mother and partner)			**Dominant**		**Dominant**		£1,042.78
Incremental cost per QALY			**Dominant**		**Dominant**		£1,940.76
Return on investment							
ROI1 one year after delivery			-0.97		-0.98		-1.03
ROI1 offspring and mother lifetime			-0.41		-0.51		-0.72
ROI1 household lifetime			0.79		0.40		-0.72
ROI2 one year after delivery			-0.18		-0.36		-0.03
ROI2 offspring and mother lifetime			9.75		7.50		10.45
ROI2 household lifetime			12.02		9.25		10.45

Table 7.12: Deterministic outcomes of the hypothetical interventions (Cautious-case)

	Control	SFH3m Cautious-case		SFH12m Cautious-case		RSDP Cautious-case	
End of pregnancy		**Experimental**	**Incremental**	**Experimental**	**Incremental**	**Experimental**	**Incremental**
Number of quitters/reducers (mother only)	88.00	317.90	229.90	317.90	229.90	514.98	514.98
Number of foetuses lost	102.23	95.60	-6.63	95.60	-6.63	102.23	94.11
Number of infants born prematurely	69.05	67.37	-1.68	67.37	-1.68	69.05	69.08
Number of infants born with LBW	99.47	89.41	-10.06	89.41	-10.06	99.47	93.74
Expected QALYs per mother	0.6348	0.6436	0.0088	0.6436	0.0088	0.6438	0.0089
Expected cost per mother and infant	£7,193.65	£8,294.03	£1,053.18	£8,529.51	£1,335.86	£7,973.76	£780.11
Incremental cost per QALY			£119,983.57		£152,187.34		£87,271.27
End of one year after delivery							
Number of quitters (mother only)	139.96	198.11	58.15	248.96	109.00	167.12	27.16
Expected LYs per mother and infant	2.5376	2.5480	0.0104	2.5480	0.0104	2.5499	0.0123
Expected QALYs per mother and infant	2.3439	2.3649	0.0209	2.3664	0.0225	2.3691	0.0252
Incremental cost per QALY	£7,602.73	£8,669.39	£1,019.46	£8,901.48	£1,298.75	£8,355.31	£752.58
Expected cost per mother and infant			£48,727.36		£57,803.60		£29,914.41
Offspring age 15 (end of childhood)							
Number of SID	1.42	1.33	-0.10	1.33	-0.10	1.32	-0.11
Expected LYs per child	10.2800	10.3604	0.0804	10.3604	0.0804	10.3751	0.0951
Expected QALYs per child	10.0483	10.1477	0.0994	10.1485	0.1001	10.1611	0.1128
Expected cost per child	£7,283.86	£8,053.19	£722.13	£8,277.08	£993.22	£7,747.05	£463.19
Incremental cost per additional QALY			£7,262.22		£9,918.14		£4,105.56
Mother and offspring lifetime combined							
Expected life years	49.2080	49.4247	0.2168	49.4376	0.2296	49.4426	0.2346
Expected QALYs	44.0641	44.3279	0.2637	44.3567	0.2926	44.3439	0.2798
Expected cost	£36,136.47	£36,795.61	£611.94	£36,917.83	£781.36	£36,653.15	£516.67
Cost per quitter/reducer at delivery (mother only)			£2,661.75		£3,398.67		£1,003.29
Incremental cost per QALY			£2,320.24		£2,670.62		£1,846.58
Mother, partner and offspring lifetime combined							
Number of quitters/reducers at delivery (mother and partner)	122.00	407.90	285.90	407.90	285.90	514.98	514.98
Expected LYs	73.9208	74.2272	0.3064	74.2404	0.3196	74.1554	0.2346
Expected QALYs	66.3108	66.6129	0.3021	66.6424	0.3316	66.5906	0.2798
Expected cost	£63,099.30	£62,290.39	-£856.11	£62,408.06	-£691.24	£63,615.98	£516.67
Cost per quitter/reducer (mother and partner)			**Dominant**		**Dominant**		£1,003.29
Incremental cost per QALY			**Dominant**		**Dominant**		£1,846.58
Return on investment							
ROI1 one year after delivery			-0.98		-0.98		-1.03
ROI1 offspring and mother lifetime			-0.59		-0.59		-0.71
ROI1 household lifetime			0.82		0.52		-0.71
ROI2 one year after delivery			-0.38		-0.47		0.00
ROI2 offspring and mother lifetime			7.02		6.05		10.76
ROI2 household lifetime			9.54		8.04		10.76

In the RSDP intervention, 697 women in the base-case and 514 in the cautious-case reduced cigarette consumption by 50%. Similar to the cessation interventions, the ICERs at delivery estimated for RSDP are significantly higher than the NICE threshold. One year after delivery, however, it is just above the threshold in the base-case (£30,853) and just below it in the cautious scenario (£29,915). The RSDP intervention generates 38 additional quitters one year after delivery in the base-case scenario and 27 in the cautious-case, indicating that reducing SDP would increase the number of quitters in addition to reducing adverse health outcomes during pregnancy.

The RSDP intervention is cost-effective according to the lifetime analyses, with an ICER of £1,941 base-case and £1,847 in the cautious-case. Despite the relatively greater QALY gains in the base-case (0.3928) compared to those in the cautious-case (0.2798), the ICER in the cautious-case scenario is lower because of the lower costs associated with fewer number of vouchers provided for women who reduce smoking. The household estimates for the RSDP intervention are the same as mother and offspring lifetime estimations since it is assumed that RSDP does not have any impact on partners.

According to the ROI analyses, none of the interventions provide a positive return on investment one year after delivery or over the lifetime when only the NHS savings are considered. However, they provide positive ROI when health gains are taken into account. For example, SFH3m generates £12.02 and £9.52 for every £1 spent per household in the base-case and cautious-case scenarios respectively.

Figures 7.1 and 7.2 below illustrate the household cost-effectiveness estimates for the hypothetical interventions in the cautious-case and base-case scenarios respectively. According to that the incremental results for SFH3m and SFH12m fall into the south-east quadrant of the cost-effectiveness plane, and hence they are dominant over the control, whereas the results for RSDP falls into the north-east quadrant, suggesting it is cost-effective with an ICER that is significantly lower than the national threshold.

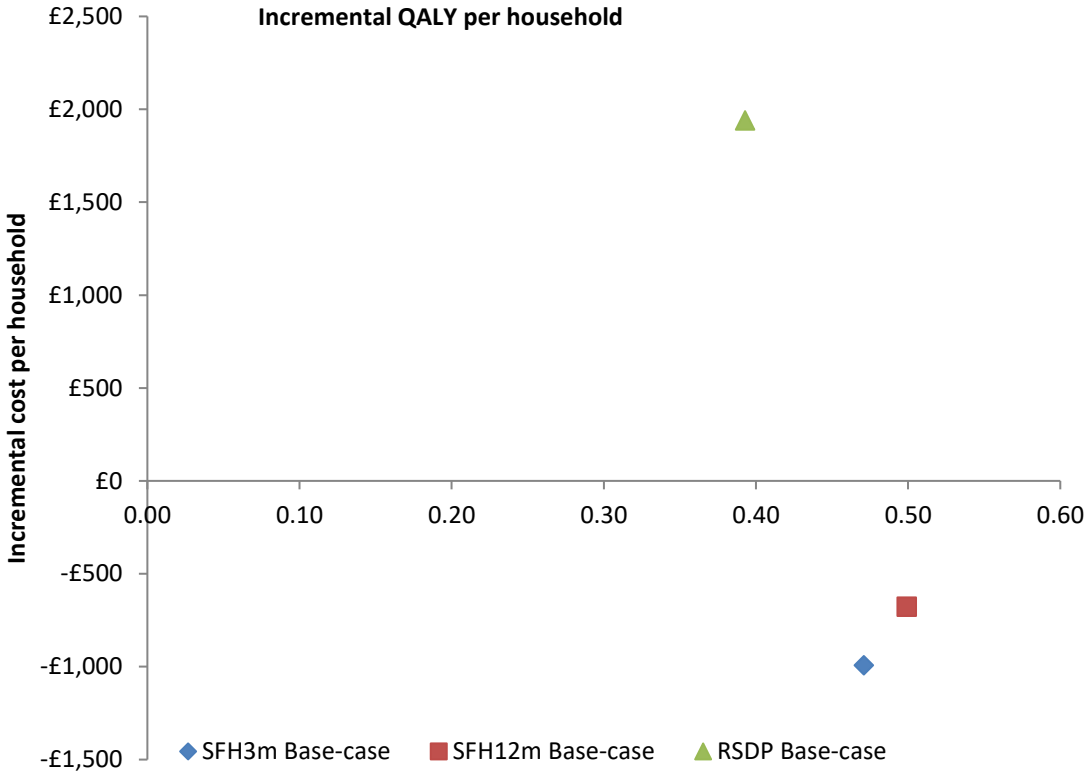


Figure 7.1: The hypothetical interventions on CE plane (Base-case)

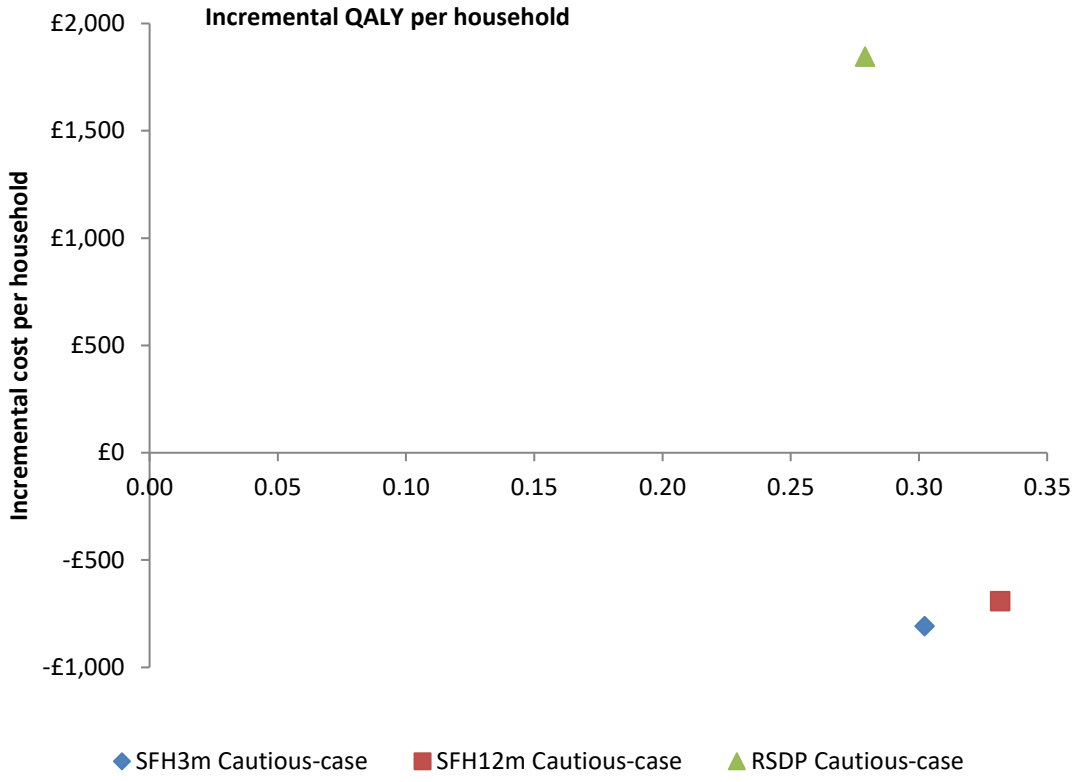


Figure 7.2:The hypothetical interventions on CE plane (Cautious-case)

7.4.2 Probabilistic Sensitivity Analysis

A PSA was conducted, following the methods described in Section 5.2.7.2. Model convergence was reached at 1,000 iterations. Outputs of the PSA are provided in Tables 7.13 to 7.15 for the base-case scenario and in Tables 7.16 to 7.18 for the cautious-case scenario.

The hypothetical interventions SFH3m and SFH12m generate 349 additional quitters at delivery and 108 and 143 additional quitters one year after delivery respectively. However, none of the interventions are cost-effective at delivery or one year after delivery at £30,000 WTP. The interventions become cost-effective when the childhood

impacts on the offspring are also considered, and they are dominant over the control if a household approach is adopted in the estimates. Similarly, the RSDP intervention is cost-effective according to the lifetime analyses although that is not the case when only the outcomes during pregnancy or until one year after delivery are considered. Thus, the cost-effectiveness outcome changes depending on the chosen time period and the inclusion of partners.

All the differences between the hypothetical interventions and the control are statistically significant with one exception. In the cautious case, the CI for the incremental cost per household for the SFH12m intervention (-£242 95% CI, -£807 to £170) suggests that there is a probability that the intervention is cost-effective but not cost-saving.

Table 7.13: PSA results for SFH3m (Base-case)

	Control (PSA)			Experimental outcomes (PSA)			Incremental outcomes (PSA)		
End of pregnancy	**Mean**	**95% CI**		**Mean**	**95% CI**		**Mean**	**95% CI**	
Number of quitters (mother only)	87.57	74.34	102.39	437.02	373.02	506.35	349.45	291.81	416.70
Number of infants lost	102.16	100.17	104.87	92.03	84.52	96.61	-10.13	-16.20	-6.22
Number of infants born prematurely	69.44	68.79	70.07	66.77	65.54	67.96	-2.67	-3.72	-1.77
Number of infants born with LBW	99.74	98.42	101.08	84.27	80.83	87.58	-15.47	-18.71	-12.58
Expected QALYs per mother	0.6349	0.6219	0.6446	0.6483	0.6352	0.6589	0.0134	0.0099	0.0180
Incremental cost per mother and offspring	£6,444.94	£3,492.11	£11,479.38	£7,716.51	£4,743.10	£12,781.93	£1,271.57	£1,078.18	£1,508.24
Incremental cost per QALY									£94,861.38
End of one year after delivery									
Number of quitters (mother)	136.65	122.80	153.20	244.53	206.62	289.52	107.88	74.17	151.58
Expected LYs per mother and infant	2.5377	2.5336	2.5408	2.5535	2.5467	2.5644	0.0159	0.0101	0.0249
Expected QALYs per mother and infant	2.3428	2.3020	2.3730	2.3753	2.3366	2.4046	0.0325	0.0231	0.0448
Expected cost per mother and infant	£6,859.90	£3,880.56	£11,857.01	£8,012.90	£5,058.54	£13,043.48	£1,153.00	£969.32	£1,367.49
Incremental cost per QALY									£35,433.78
Offspring age 15 (end of childhood)									
Number of SID	1.43	1.18	1.79	1.29	1.12	1.51	-0.15	-0.31	-0.01
Expected LYs per child	10.2765	10.2436	10.3009	10.3995	10.3458	10.4856	0.1231	0.0784	0.1938
Expected QALYs per child	10.0342	9.6698	10.2310	10.1891	9.8640	10.3758	0.1549	0.0909	0.2467
Expected cost per child	£7,318.03	£4,704.70	£12,214.61	£7,978.86	£5,403.93	£13,033.86	£660.83	£338.15	£925.16
Incremental cost per additional QALY									£4,265.94
Mother and offspring lifetime combined									
Expected LYs	49.1483	49.0309	49.2731	49.4853	49.3127	49.7235	0.3370	0.2234	0.5111
Expected QALYs	44.1364	43.4348	44.6986	44.5531	43.8639	45.1311	0.4167	0.2852	0.6075
Expected cost	£35,494.16	£31,925.04	£40,697.04	£35,962.99	£32,381.34	£41,066.43	£468.83	£92.99	£778.13
Incremental cost per quitter at delivery (mother)									£1,341.62
Incremental cost per QALY									£1,125.21
HOUSEHOLD									
Number of quitters at delivery (mother and partner)	121.61	106.72	137.94	587.08	518.72	662.77	465.47	403.52	535.57
Expected LYs	73.8482	73.6645	74.0235	74.2810	74.0567	74.5687	0.4328	0.3062	0.6183
Expected QALYs	66.3655	65.3373	67.1626	66.8056	65.7788	67.6120	0.4401	0.2986	0.6423
Expected cost	£62,500.72	£58,341.78	£68,105.60	£61,434.84	£57,300.19	£66,979.12	-£1,065.88	-£1,838.31	-£533.87
Incremental cost per quitter (mother and partner)									**Dominant**
Incremental cost per QALY									**Dominant**
Return on investment									
ROI1 one year after delivery							-0.92	-1.00	-0.86
ROI1 offspring and mother lifetime							-0.37	-0.58	-0.08
ROI1 household lifetime							0.86	0.39	1.50
ROI2 one year after delivery							-0.14	-0.36	0.16
ROI2 offspring and mother lifetime							9.62	6.32	14.45
ROI2 household lifetime							11.42	7.76	16.37

Table 7.14: PSA Results for SFH12m (Base-case)

	Control (PSA)			Experimental outcomes (PSA)			Incremental outcomes (PSA)		
End of pregnancy	**Mean**	**95% CI**		**Mean**	**95% CI**		**Mean**	**95% CI**	
Number of quitters (mother only)	88.09	75.81	101.79	437.59	374.14	505.83	349.49	295.01	410.80
Number of infants lost	102.18	100.07	104.96	92.02	83.82	96.83	-10.16	-16.90	-6.33
Number of infants born prematurely	69.42	68.74	70.05	66.71	65.37	67.88	-2.72	-3.74	-1.85
Number of infants born with LBW	99.72	98.32	101.12	84.23	80.63	87.26	-15.49	-18.54	-12.89
Expected QALYs per mother	0.6346	0.6213	0.6447	0.6480	0.6342	0.6585	0.0134	0.0100	0.0179
Incremental cost per mother and offspring	£6,458.68	£3,460.92	£11,628.61	£8,149.11	£5,056.64	£13,441.80	£1,690.42	£1,408.11	£2,012.02
Incremental cost per QALY									£125,842.05
End of one year after delivery									
Number of quitters (mother only)	136.61	122.32	152.63	279.32	239.45	329.77	142.71	106.71	188.31
Expected LYs per mother and infant	2.5376	2.5336	2.5407	2.5536	2.5464	2.5656	0.0159	0.0102	0.0258
Expected QALYs per mother and infant	2.3425	2.3046	2.3715	2.3761	2.3405	2.4053	0.0335	0.0245	0.0463
Expected cost per mother and infant	£6,866.35	£3,864.47	£12,011.73	£8,461.77	£5,345.37	£13,732.13	£1,595.42	£1,297.47	£1,921.76
Incremental cost per QALY									£47,565.50
Offspring age 15 (end of childhood)									
Number of SID	1.43	1.18	1.83	1.28	1.12	1.50	-0.14	-0.33	-0.01
Expected LYs per child	10.2762	10.2432	10.3006	10.3998	10.3427	10.4930	0.1235	0.0796	0.2006
Expected QALYs per child	10.0378	9.6979	10.2316	10.1930	9.8916	10.3761	0.1553	0.0950	0.2484
Expected cost per child	£7,308.95	£4,678.73	£12,434.75	£8,408.84	£5,814.49	£13,535.83	£1,099.88	£677.98	£1,490.92
Incremental cost per additional QALY									£7,082.95
Mother and offspring lifetime combined									
Expected LYs	49.1511	49.0294	49.2815	49.4984	49.3155	49.7369	0.3472	0.2358	0.5348
Expected QALYs	44.1318	43.4696	44.6859	44.5685	43.8891	45.1691	0.4367	0.3055	0.6310
Expected cost	£35,498.85	£31,708.90	£40,867.88	£36,338.29	£32,531.88	£41,599.41	£839.44	£363.79	£1,304.97
Incremental cost per quitter at delivery (mother)									£2,401.86
Incremental cost per QALY									£1,922.12
HOUSEHOLD									
Number of quitters at delivery (mother and partner)	121.92	108.13	136.42	586.60	516.66	661.30	464.68	407.27	528.61
Expected LYs	73.8541	73.6783	74.0468	74.2980	74.0599	74.5926	0.4438	0.3183	0.6369
Expected QALYs	66.3545	65.3299	67.1694	66.8160	65.7625	67.6488	0.4616	0.3218	0.6610
Expected cost	£62,478.09	£57,866.28	£68,389.79	£61,768.43	£57,037.44	£67,752.37	-£709.66	-£1,565.13	-£83.55
Incremental cost per quitter (mother and partner)									**Dominant**
Incremental cost per QALY									**Dominant**
Return on investment									
ROI1 one year after delivery							-0.95	-1.01	-0.90
ROI1 offspring and mother lifetime							-0.50	-0.69	-0.25
ROI1 household lifetime							0.44	0.05	1.04
ROI2 one year after delivery							-0.35	-0.55	-0.07
ROI2 offspring and mother lifetime							7.40	4.49	11.55
ROI2 household lifetime							8.78	5.56	13.28

Table 7.15: PSA results of RSDP (Base-case)

	Control (PSA)			Experimental outcomes (PSA)			Incremental outcomes (PSA)		
End of pregnancy	**Mean**	**95% CI**		**Mean**	**95% CI**		**Mean**	**95% CI**	
Number of reducers (mothers only)	0.00	0.00	0.00	730.40	630.78	831.46	730.40	630.78	831.46
Number of infants lost	102.21	99.98	105.19	90.65	89.01	92.11	-11.56	-13.64	-10.00
Number of infants born prematurely	69.41	68.78	70.02	69.21	68.67	69.73	-0.20	-0.40	0.00
Number of infants born with LBW	99.69	98.32	101.01	91.53	90.62	92.41	-8.16	-9.28	-7.09
Expected QALYs per mother	0.6349	0.6222	0.6452	0.6476	0.6339	0.6587	0.0127	0.0077	0.0178
Incremental cost per mother and offspring	£6,583.53	£3,547.85	£11,882.06	£7,760.60	£4,720.97	£13,123.42	£1,177.07	£1,008.13	£1,361.51
Incremental cost per QALY									£92,914.78
End of one year after delivery									
Number of quitters (mothers only)	136.85	122.40	154.44	175.38	151.71	205.23	38.53	26.72	53.70
Expected LYs per mother and infant	2.5376	2.5332	2.5410	2.5551	2.5529	2.5576	0.0175	0.0152	0.0205
Expected QALYs per mother and infant	2.3432	2.3037	2.3735	2.3787	2.3400	2.4101	0.0355	0.0239	0.0484
Expected cost per mother and infant	£7,000.93	£3,945.07	£12,277.07	£8,125.96	£5,048.68	£13,533.81	£1,125.04	£954.72	£1,307.48
Incremental cost per QALY									£31,648.96
Offspring age 15 (end of childhood)									
Number of SID	1.43	1.19	1.79	1.28	1.07	1.60	-0.15	-0.19	-0.12
Expected LYs per child	10.2759	10.2412	10.3024	10.4120	10.3940	10.4320	0.1361	0.1179	0.1601
Expected QALYs per child	10.0308	9.6888	10.2373	10.1955	9.8843	10.3742	0.1648	0.1305	0.2184
Expected cost per child	£7,456.47	£4,685.97	£13,403.06	£8,131.20	£5,385.45	£14,085.14	£674.73	£366.59	£949.80
Incremental cost per additional QALY									£4,095.26
Mother and offspring lifetime combined									
Expected LYs	49.1520	49.0252	49.2779	49.4884	49.3756	49.6040	0.3365	0.2915	0.3926
Expected QALYs	44.1366	43.4258	44.6835	44.5424	43.8845	45.0716	0.4058	0.3360	0.4938
Expected cost	£35,591.31	£31,778.83	£41,381.18	£36,331.37	£32,491.75	£42,268.77	£740.06	£428.74	£1,028.88
Incremental cost per reducer at delivery (mother)									£1,013.22
Incremental cost per QALY									£1,823.91
HOUSEHOLD									
Number of reducers (mother)	0.00	0.00	0.00	730.40	630.78	831.46	730.40	630.78	831.46
Expected LYs	73.8542	73.6765	74.0414	74.1907	74.0159	74.3612	0.3365	0.2915	0.3926
Expected QALYs	66.3656	65.3216	67.1591	66.7714	65.7364	67.5642	0.4058	0.3360	0.4938
Expected cost	£62,546.17	£57,898.84	£68,757.98	£63,286.23	£58,466.12	£69,465.83	£740.06	£428.74	£1,028.88
Incremental cost per reducer at delivery (mother)									£1,013.22
Incremental cost per QALY									£1,823.91
Return on investment									
ROI1 one year after delivery							-1.01	-1.08	-0.97
ROI1 offspring and mother lifetime							-0.66	-0.86	-0.41
ROI1 household lifetime							-0.66	-0.86	-0.41
ROI2 one year after delivery							-0.05	-0.38	0.34
ROI2 offspring and mother lifetime							10.30	7.62	13.32
ROI2 household lifetime							10.30	7.62	13.32

Table 7.16: PSA results for SFH3m (Cautious-case)

	Control			SHF3m			Incremental outcomes		
End of pregnancy	**Mean**	**95% CI**		**Mean**	**95% CI**		**Mean**	**95% CI**	
Number of quitters (mothers only)	88.08	75.24	101.98	317.64	268.83	371.39	229.56	191.96	274.13
Number of infants lost	102.12	99.97	104.86	95.47	89.83	99.49	-6.65	-10.68	-4.01
Number of infants born prematurely	69.42	68.82	70.05	67.75	66.67	68.69	-1.67	-2.49	-1.04
Number of infants born with LBW	99.72	98.38	101.10	89.67	86.93	92.36	-10.04	-12.65	-8.05
Expected QALYs per mother	0.6346	0.6208	0.6444	0.6434	0.6292	0.6533	0.0088	0.0065	0.0117
Incremental cost per mother and offspring	£6,554.95	£3,520.68	£11,765.31	£7,609.87	£4,581.77	£12,929.19	£1,054.92	£882.78	£1,262.16
Incremental cost per QALY									£119,463.27
End of one year after delivery									
Number of quitters (mothers only)	136.40	122.48	153.15	182.65	156.82	218.00	46.25	28.74	77.68
Expected LYs per mother and infant	2.5377	2.5337	2.5409	2.5482	2.5422	2.5566	0.0104	0.0065	0.0164
Expected QALYs per mother and infant	2.3428	2.3043	2.3729	2.3635	2.3258	2.3934	0.0206	0.0146	0.0291
Expected cost per mother and infant	£6,970.81	£3,964.64	£12,179.18	£7,962.38	£4,940.64	£13,230.34	£991.57	£811.68	£1,199.74
Incremental cost per QALY									£48,039.69
Offspring age 15 (end of childhood)									
Number of SID	1.43	1.19	1.81	1.33	1.13	1.64	-0.10	-0.22	-0.01
Expected LYs per child	10.2769	10.2453	10.3023	10.3578	10.3104	10.4238	0.0809	0.0499	0.1287
Expected QALYs per child	10.0415	9.6931	10.2355	10.1430	9.8229	10.3265	0.1015	0.0595	0.1603
Expected cost per child	£7,394.19	£4,617.45	£12,600.75	£8,056.67	£5,319.97	£13,428.21	£662.48	£398.62	£932.10
Incremental cost per additional QALY									£6,527.78
Mother and offspring lifetime combined									
Expected LYs	49.1528	49.0283	49.2824	49.3673	49.2129	49.5591	0.2145	0.1374	0.3344
Expected QALYs	44.1445	43.3947	44.7141	44.4041	43.6751	44.9707	0.2597	0.1741	0.3884
Expected cost	£35,574.38	£32,105.23	£40,989.71	£36,161.91	£32,662.19	£41,754.22	£587.54	£277.11	£886.06
Incremental cost per quitter at delivery (mother)									£2,556.88
Incremental cost per QALY									£2,262.77
HOUSEHOLD									
Number of quitters at delivery (mother and partner)	122.15	107.13	137.49	407.81	354.37	462.04	285.66	244.34	333.62
Expected LYs	73.8514	73.6580	74.0240	74.1284	73.9084	74.3632	0.2770	0.1904	0.3967
Expected QALYs	66.3704	65.2518	67.1981	66.6473	65.5391	67.4494	0.2769	0.1874	0.4064
Expected cost	£62,588.64	£58,188.14	£68,348.49	£62,175.32	£57,679.99	£67,937.03	-£413.33	-£932.80	-£15.65
Incremental cost per quitter (mother and partner)									**Dominant**
Incremental cost per QALY									**Dominant**
Return on investment									
ROI1 one year after delivery							-0.95	-1.02	-0.89
ROI1 offspring and mother lifetime							-0.56	-0.76	-0.30
ROI1 household lifetime							0.41	0.01	0.96
ROI2 one year after delivery							-0.35	-0.57	-0.06
ROI2 offspring and mother lifetime							6.99	4.12	11.35
ROI2 household lifetime							8.45	5.33	13.20

Table 7.17: PSA results for SFH12m (Cautious-case)

	Control (PSA)			Experimental outcomes (PSA)			Incremental outcomes (PSA)		
End of pregnancy	**Mean**	**95% CI**		**Mean**	**95% CI**		**Mean**	**95% CI**	
Number of quitters (mother only)	88.11	74.72	102.93	318.49	271.74	367.00	230.38	191.28	270.18
Number of infants lost	102.12	99.94	105.56	95.40	89.68	99.56	-6.72	-10.74	-4.02
Number of infants born prematurely	69.44	68.82	70.05	67.76	66.78	68.71	-1.68	-2.35	-1.14
Number of infants born with LBW	99.75	98.40	101.12	89.66	87.10	92.08	-10.09	-12.01	-8.30
Expected QALYs per mother	0.6347	0.6212	0.6452	0.6436	0.6298	0.6543	0.0088	0.0064	0.0118
Incremental cost per mother and offspring	£6,614.52	£3,601.91	£12,487.38	£7,945.80	£4,904.90	£13,999.69	£1,331.28	£1,129.07	£1,551.13
Incremental cost per QALY									£150,456.49
End of one year after delivery									
Number of quitters (mother only)	136.24	122.32	151.90	231.10	204.78	260.37	94.86	74.98	119.11
Expected LYs per mother and infant	2.5377	2.5329	2.5411	2.5482	2.5421	2.5566	0.0105	0.0065	0.0165
Expected QALYs per mother and infant	2.3430	2.3041	2.3744	2.3650	2.3284	2.3950	0.0220	0.0158	0.0305
Expected cost per mother and infant	£7,031.05	£4,000.55	£12,921.11	£8,293.77	£5,241.20	£14,268.54	£1,262.72	£1,053.50	£1,482.84
Incremental cost per QALY									£57,277.59
Offspring age 15 (end of childhood)									
Number of SID	1.42	1.18	1.80	1.33	1.14	1.61	-0.10	-0.21	-0.02
Expected LYs per child	10.2770	10.2389	10.3040	10.3585	10.3103	10.4250	0.0815	0.0507	0.1285
Expected QALYs per child	10.0434	9.6918	10.2354	10.1453	9.8394	10.3312	0.1019	0.0600	0.1638
Expected cost per child	£7,419.05	£4,648.34	£13,170.67	£8,354.55	£5,603.97	£14,220.82	£935.51	£641.42	£1,196.03
Incremental cost per additional QALY									£9,178.65
Mother and offspring lifetime combined									
Expected LYs	49.1527	49.0369	49.2866	49.3819	49.2338	49.5875	0.2293	0.1501	0.3491
Expected QALYs	44.1406	43.3931	44.7293	44.4286	43.7128	44.9977	0.2880	0.1964	0.4120
Expected cost	£35,630.72	£31,924.70	£41,875.80	£36,396.09	£32,654.21	£42,825.86	£765.38	£427.11	£1,062.69
Incremental cost per quitter at delivery (mother)									£3,322.22
Incremental cost per QALY									£2,657.70
HOUSEHOLD									
Number of quitters at delivery (mother and partner)	122.02	107.79	138.74	408.44	358.06	461.79	286.42	247.11	327.98
Expected LYs	73.8535	73.6645	74.0289	74.1458	73.9375	74.4048	0.2923	0.2075	0.4256
Expected QALYs	66.3614	65.2493	67.2378	66.6675	65.5855	67.5298	0.3061	0.2097	0.4365
Expected cost	£62,567.76	£58,169.89	£69,115.64	£62,326.19	£57,879.31	£68,707.43	-£241.56	-£807.16	£170.32
Incremental cost per quitter (mother and partner)									**Dominant**
Incremental cost per QALY									**Dominant**
Return on investment									
ROI1 one year after delivery							-0.96	-1.01	-0.92
ROI1 offspring and mother lifetime							-0.58	-0.74	-0.35
ROI1 household lifetime							0.19	-0.12	0.67
ROI2 one year after delivery							-0.45	-0.62	-0.23
ROI2 offspring and mother lifetime							6.03	3.73	9.15
ROI2 household lifetime							7.21	4.64	10.66

Table 7.18: PSA results of RSDP (Cautious-case)

	Control (PSA)			Experimental outcomes (PSA)			Incremental outcomes (PSA)		
End of pregnancy	**Mean**	**95% CI**		**Mean**	**95% CI**		**Mean**	**95% CI**	
Number of reducers (mothers only)	0.00	0.00	0.00	513.91	452.49	566.03	513.91	452.49	566.03
Number of infants lost	102.11	100.02	104.55	93.99	92.16	95.91	-8.11	-9.90	-6.51
Number of infants born prematurely	69.44	68.82	70.04	69.26	68.71	69.80	-0.17	-0.33	-0.03
Number of infants born with LBW	99.75	98.35	101.21	93.91	92.84	95.10	-5.84	-7.04	-4.70
Expected QALYs per mother	0.6349	0.6205	0.6449	0.6438	0.6293	0.6543	0.0089	0.0052	0.0126
Incremental cost per mother and offspring	£6,521.55	£3,685.47	£11,566.50	£7,289.68	£4,395.57	£12,450.84	£768.13	£618.98	£924.91
Incremental cost per QALY									£86,200.59
End of one year after delivery									
Number of quitters (mothers only)	136.56	122.79	152.87	163.92	143.83	187.34	27.36	18.99	38.09
Expected LYs per mother and infant	2.5377	2.5340	2.5408	2.5501	2.5471	2.5527	0.0123	0.0099	0.0149
Expected QALYs per mother and infant	2.3429	2.3044	2.3742	2.3679	2.3320	2.3986	0.0250	0.0160	0.0343
Expected cost per mother and infant	£6,937.58	£4,102.67	£12,087.52	£7,660.90	£4,759.30	£12,880.21	£723.32	£576.87	£875.03
Incremental cost per QALY									£28,890.62
Offspring age 15 (end of childhood)									
Number of SID	1.43	1.18	1.81	1.32	1.09	1.68	-0.11	-0.14	-0.08
Expected LYs per child	10.2770	10.2483	10.3020	10.3725	10.3485	10.3939	0.0956	0.0768	0.1159
Expected QALYs per child	10.0357	9.6569	10.2337	10.1515	9.8188	10.3329	0.1158	0.0874	0.1607
Expected cost per child	£7,339.62	£4,750.31	£12,118.72	£7,740.32	£5,122.63	£12,543.40	£400.70	£166.18	£614.47
Incremental cost per additional QALY									£3,461.11
Mother and offspring lifetime combined									
Expected LYs	49.1495	49.0321	49.2750	49.3858	49.2732	49.5064	0.2364	0.1905	0.2857
Expected QALYs	44.1432	43.4076	44.7130	44.4288	43.7069	44.9886	0.2856	0.2222	0.3594
Expected cost	£35,564.90	£32,106.20	£40,742.49	£36,011.73	£32,501.22	£41,284.56	£446.83	£204.02	£662.72
Incremental cost per reducer at delivery (mother)									£869.46
Incremental cost per QALY									£1,564.55
HOUSEHOLD									
Number of reducers (mother)	0.00	0.00	0.00	513.91	452.49	566.03	513.91	452.49	566.03
Expected LYs	73.8495	73.6893	74.0237	74.0859	73.9286	74.2551	0.2364	0.1905	0.2857
Expected QALYs	66.3701	65.2645	67.2417	66.6557	65.5411	67.4988	0.2856	0.2222	0.3594
Expected cost	£62,544.23	£58,083.50	£68,552.22	£62,991.05	£58,553.62	£68,935.61	£446.83	£204.02	£662.72
Incremental cost per reducer at delivery (mother)									£869.46
Incremental cost per QALY									£1,564.55
Return on investment									
ROI1 one year after delivery							-0.99	-1.07	-0.95
ROI1 offspring and mother lifetime							-0.61	-0.83	-0.32
ROI1 household lifetime							-0.61	-0.83	-0.32
ROI2 one year after delivery							0.05	-0.34	0.55
ROI2 offspring and mother lifetime							11.30	7.96	15.65
ROI2 household lifetime							11.30	7.96	15.65

The incremental cost and QALY gain calculations produced by the PSA are demonstrated in Figures 7.3 to 7.18 for the base-case scenario. All iterations in the within pregnancy analyses suggest that none of the interventions are cost-effective at delivery. The mother and offspring lifetime analyses show that there is a small probability that the SFH3m and SFH12m are dominant over the comparator. RSDP is cost-effective in the mother and offspring lifetime with some uncertainty around the incremental cost estimates. In the household analyses, all iterations fall into the south-east quadrant for SFH3m while there are few instances where the values are in the north-east quadrant for SFH12m. Thus, in the base-case scenario, SFH3m is dominant over the comparator, whereas there is a small probability that SFH12m might be cost-effective rather than dominant.

The figures show that in the lifetime estimations, at £30,000 per QALY threshold, the probability of cost-effectiveness is 100% for all the interventions although at delivery, the probability is zero. At delivery, the probability of cost-effectiveness reaches 100% around a WTP of £140,000 for SFH3m and £200,000 for SFH12m in the base-case scenario. That figure is £2,000 in the mother and offspring lifetime analyses for SFH3m and SFH12m base-case. Similarly, 100% probability is achieved at a WTP of £3,000 for RSDP base-case estimations. The household CEACs show that the interventions are always cost-effective, with a small probability of not being cost-effective if the WTP is £0.

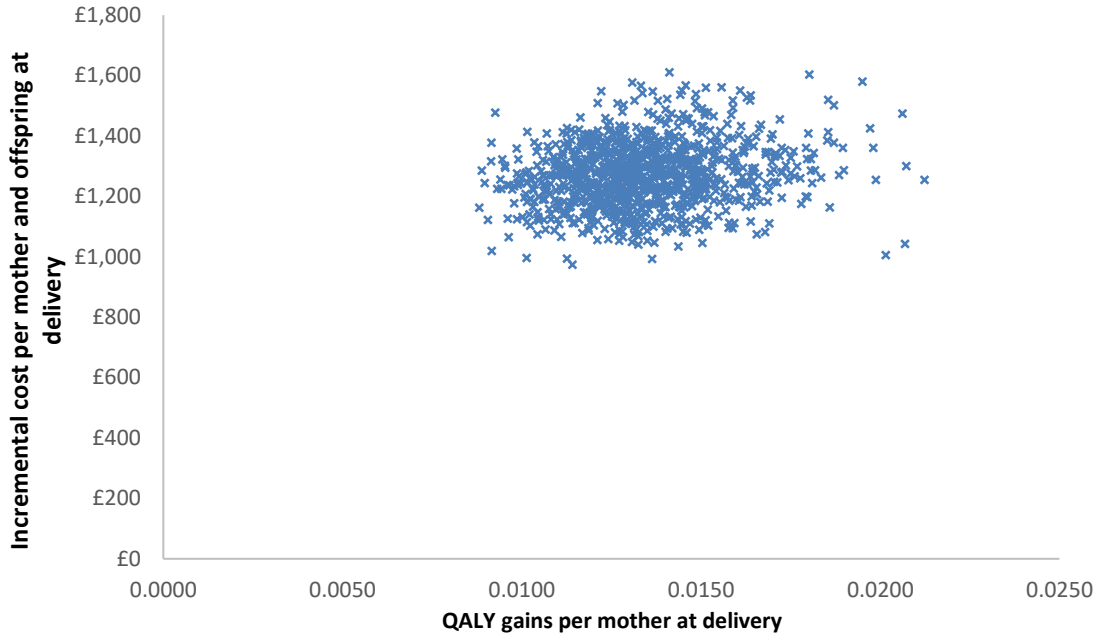


Figure 7.3: Scatterplot for incremental costs and QALY gains expected from the SFH3m base-case within pregnancy analysis

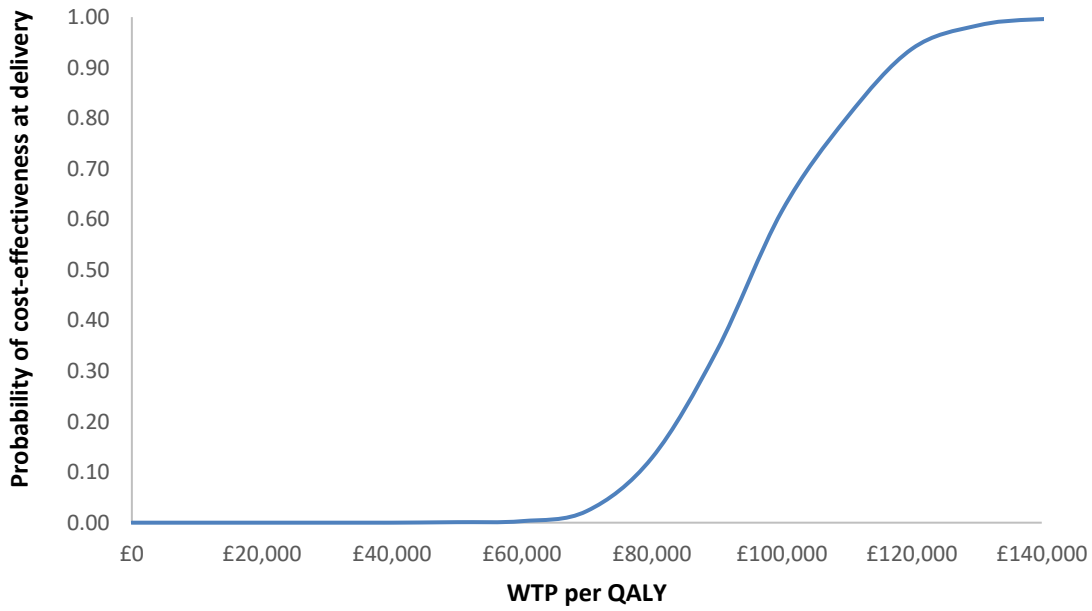


Figure 7.4: CEAC at delivery for the SFH3m base-case

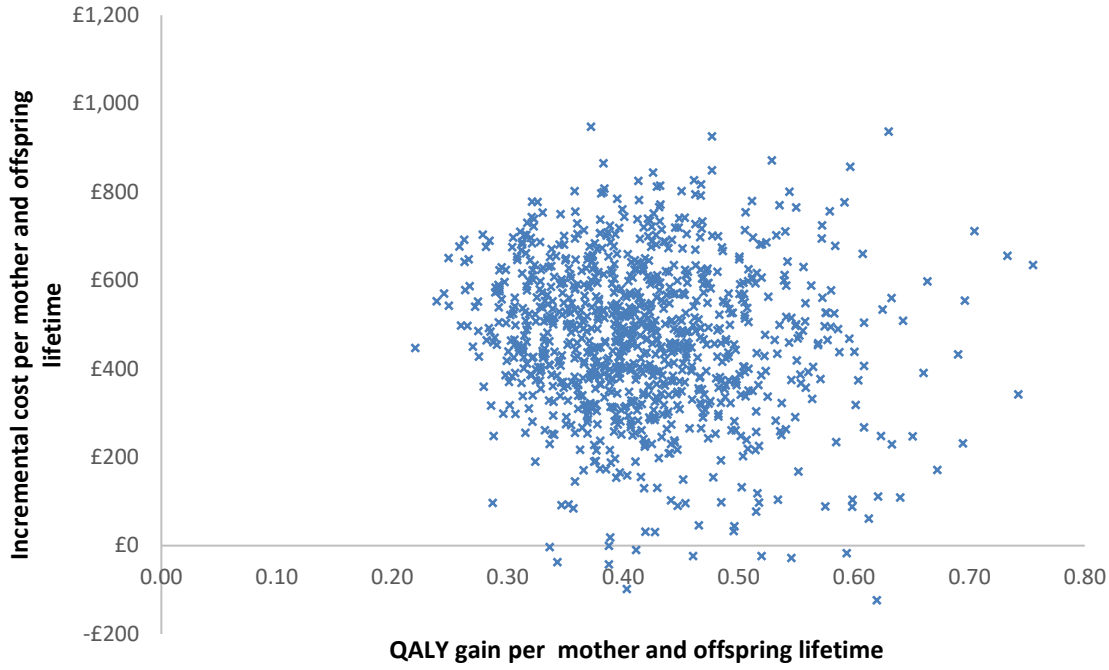


Figure 7.5: Scatterplot for incremental costs and QALY gains expected from the SFH3m base-case mother and offspring lifetime analysis

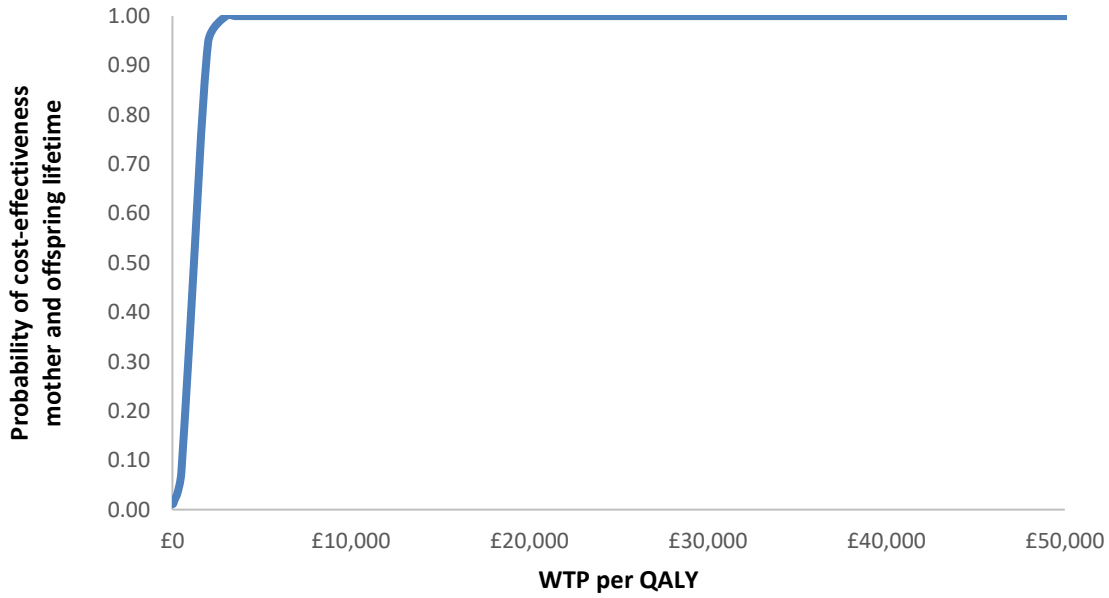


Figure 7.6: Mother and offspring lifetime CEAC for the SFH3m base-case

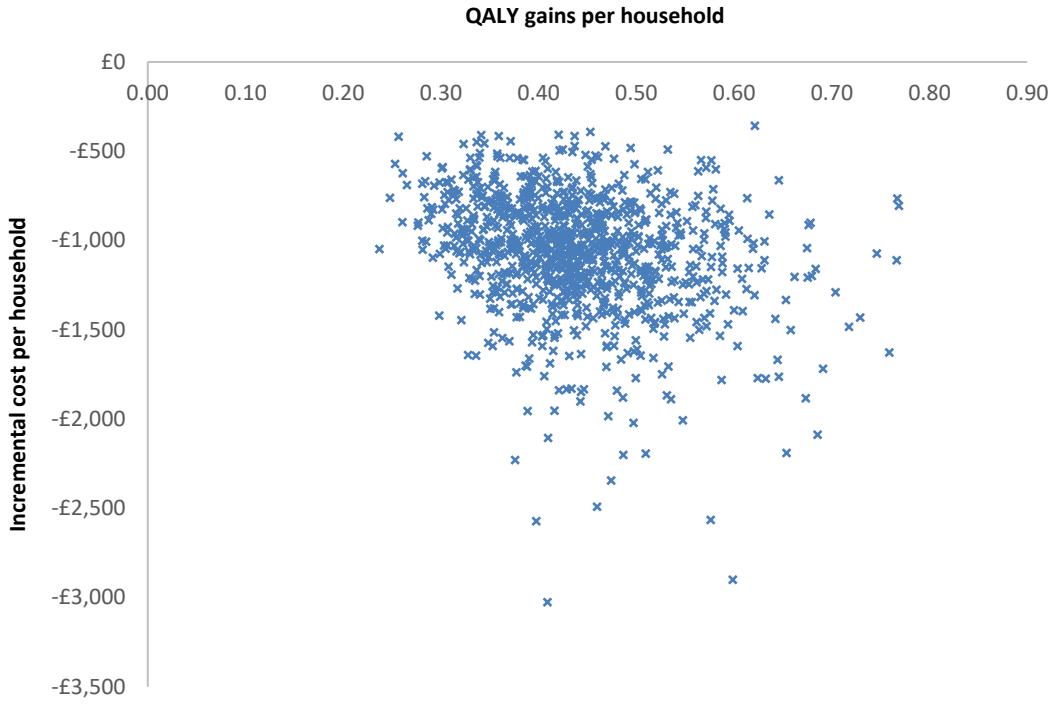


Figure 7.7: Scatterplot for incremental costs and QALY gains expected from the SFH3m base-case household analysis

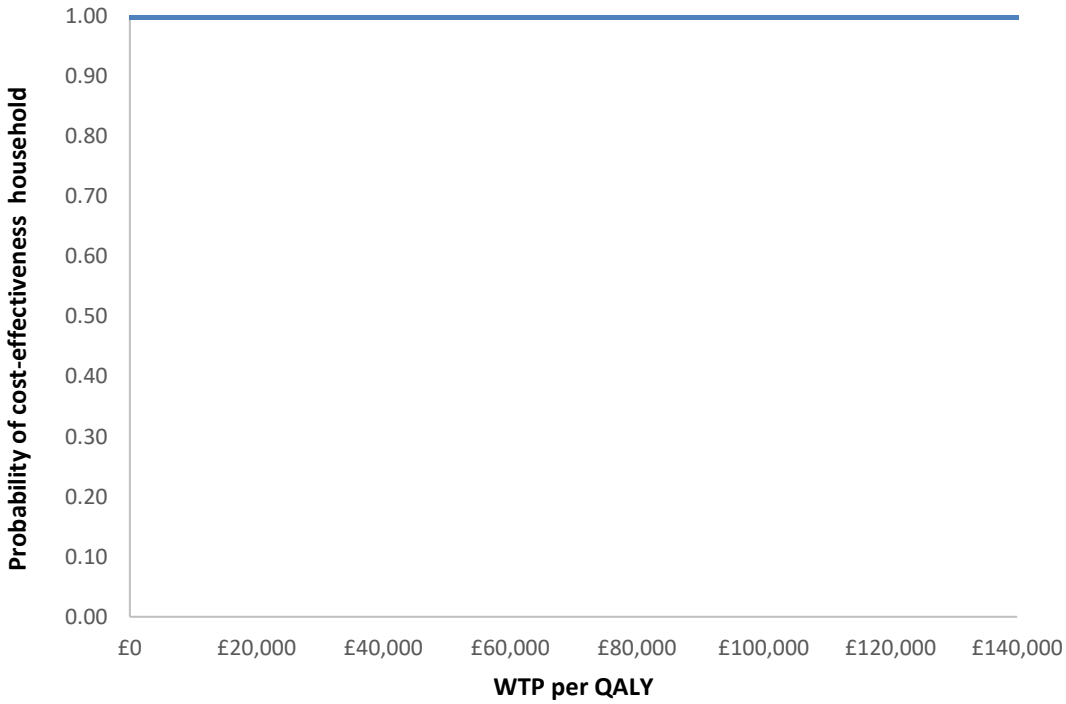


Figure 7.8: Household lifetime CEAC for the SFH3m base-case

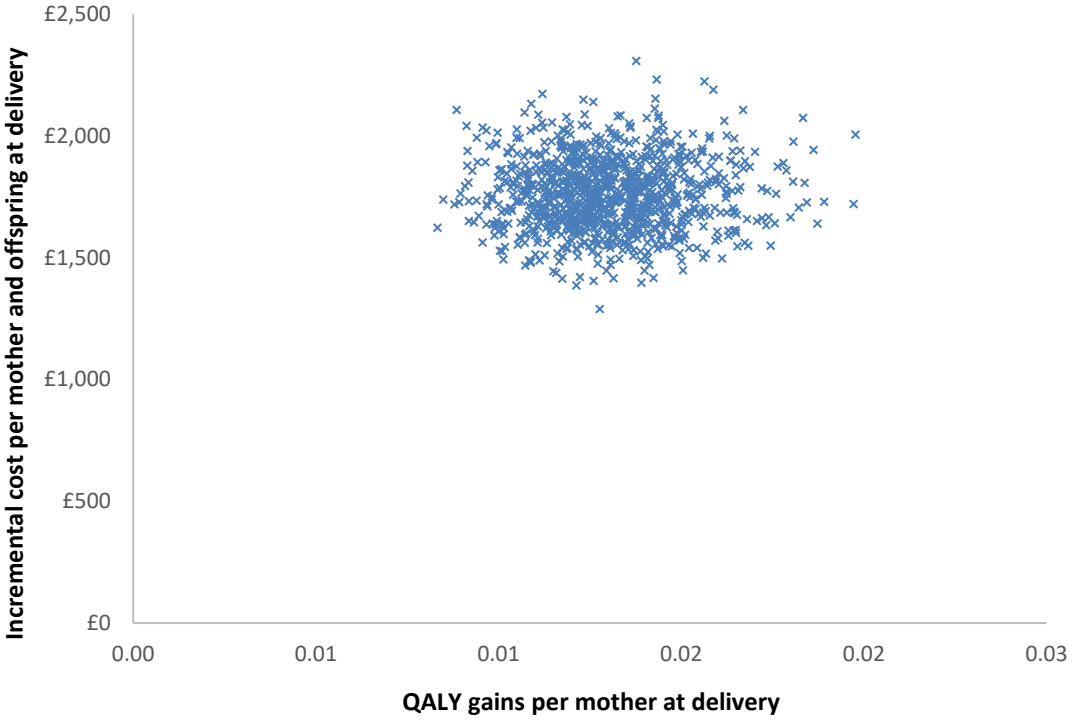


Figure 7.9: Scatterplot for incremental costs and QALY gains expected from the SFH12m base-case within pregnancy analysis

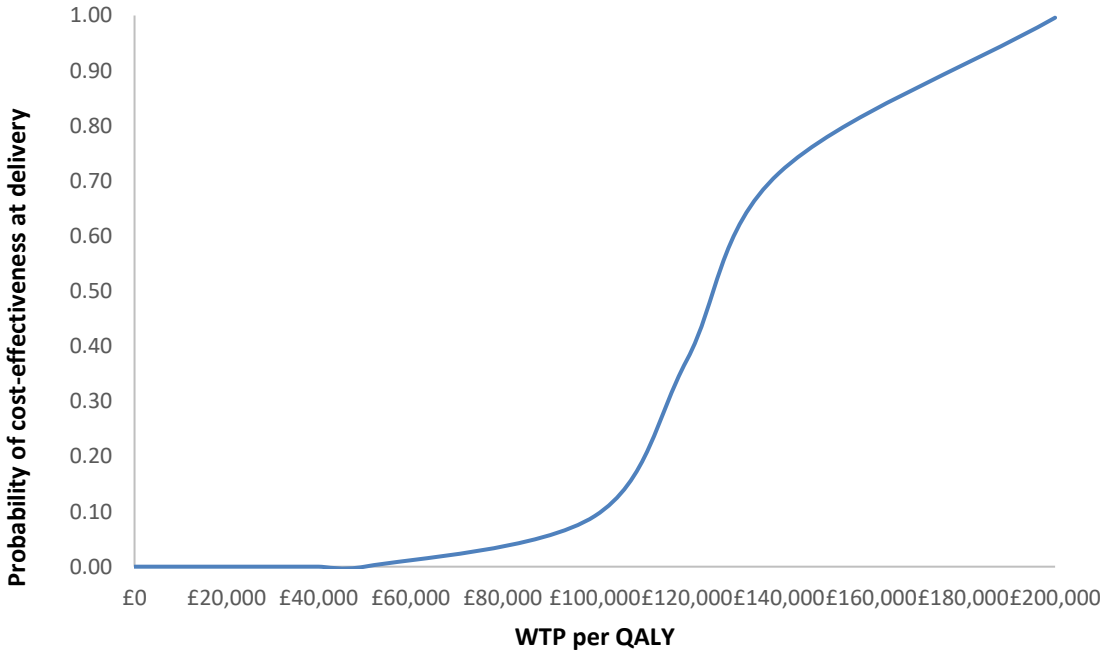


Figure 7.10: : CEAC at delivery for the SFH12m base-case

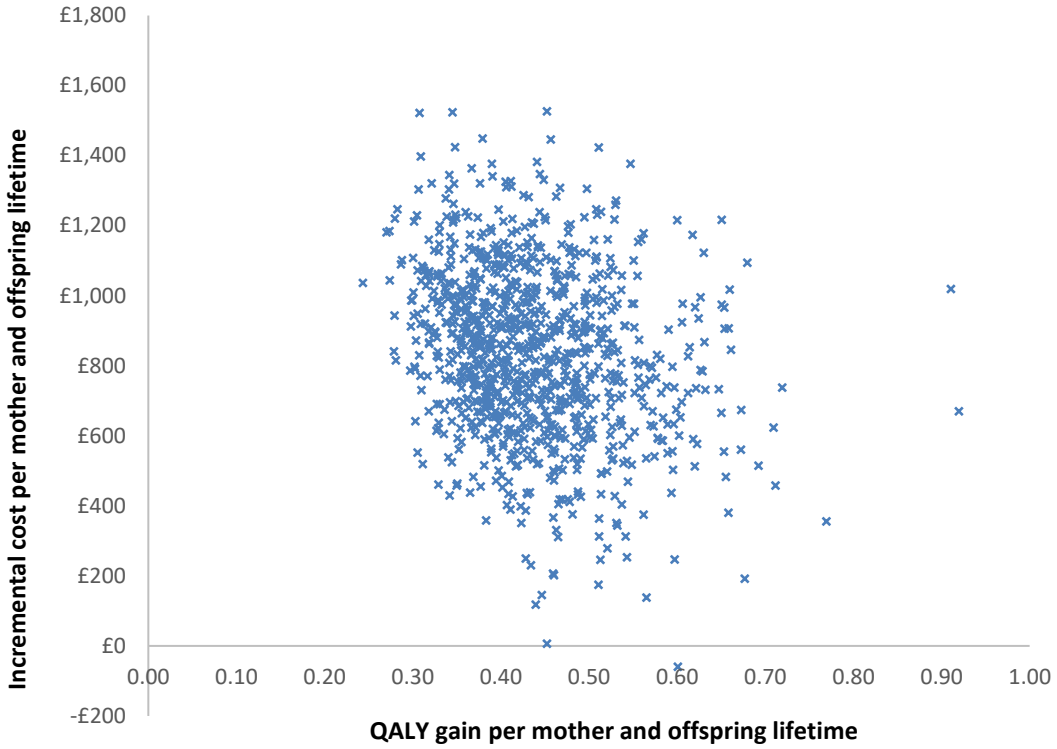


Figure 7.11: Scatterplot for incremental costs and QALY gains expected from the SFH12m base-case mother and offspring lifetime analysis

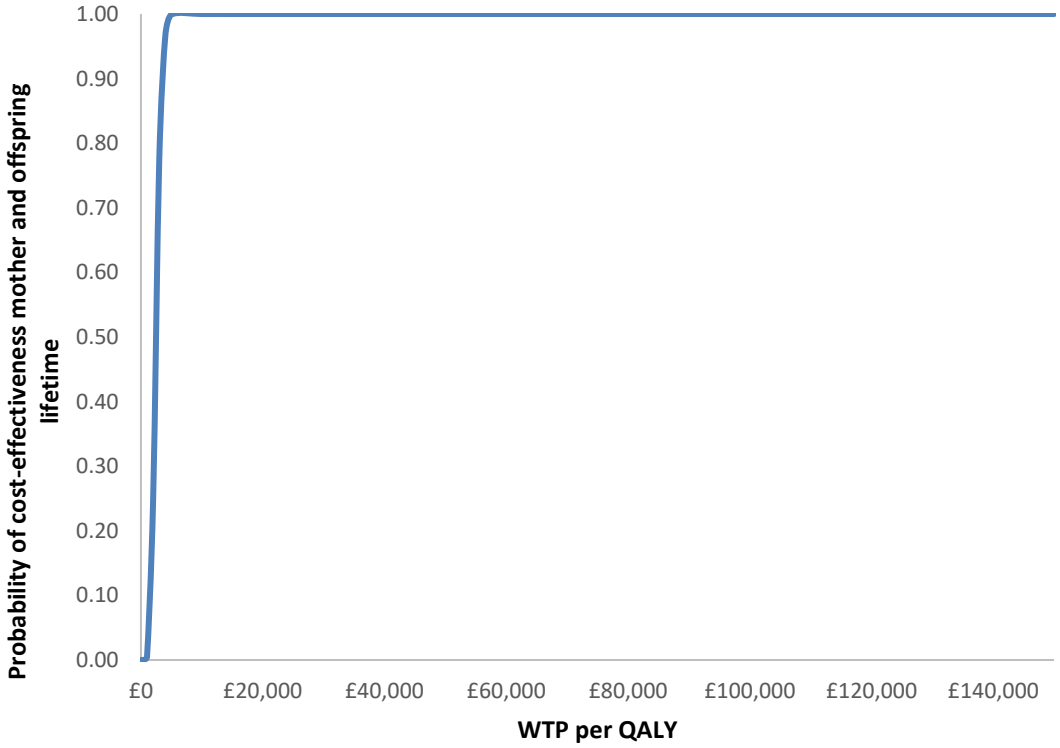


Figure 7.12: Mother and offspring lifetime CEAC for the SFH12m base-case

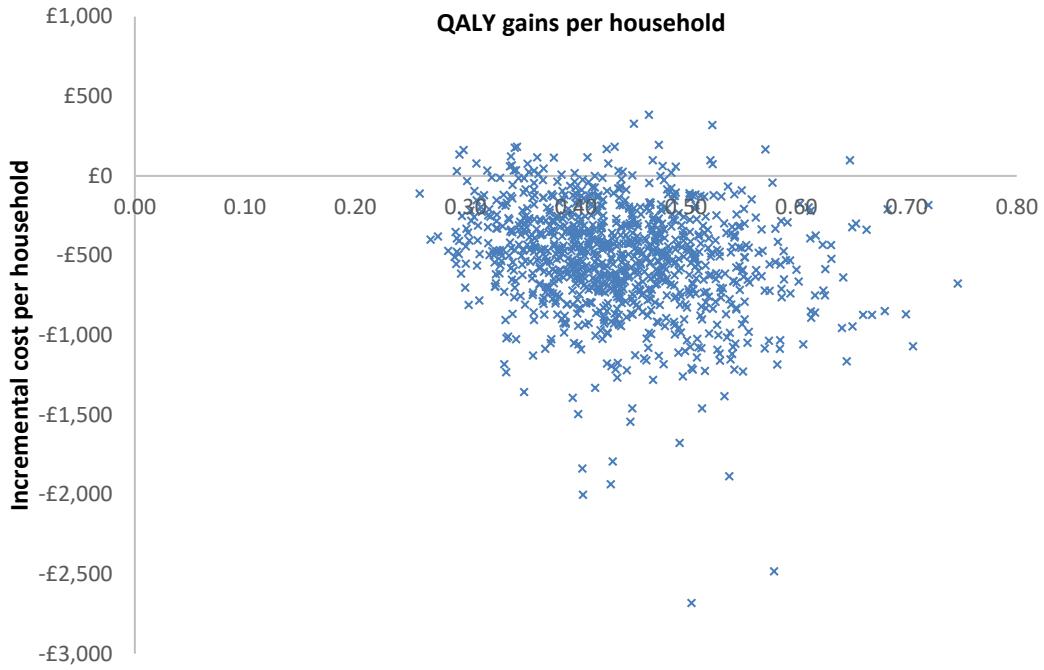


Figure 7.13: Scatterplot for incremental costs and QALY gains expected from the SFH12m base-case household analysis

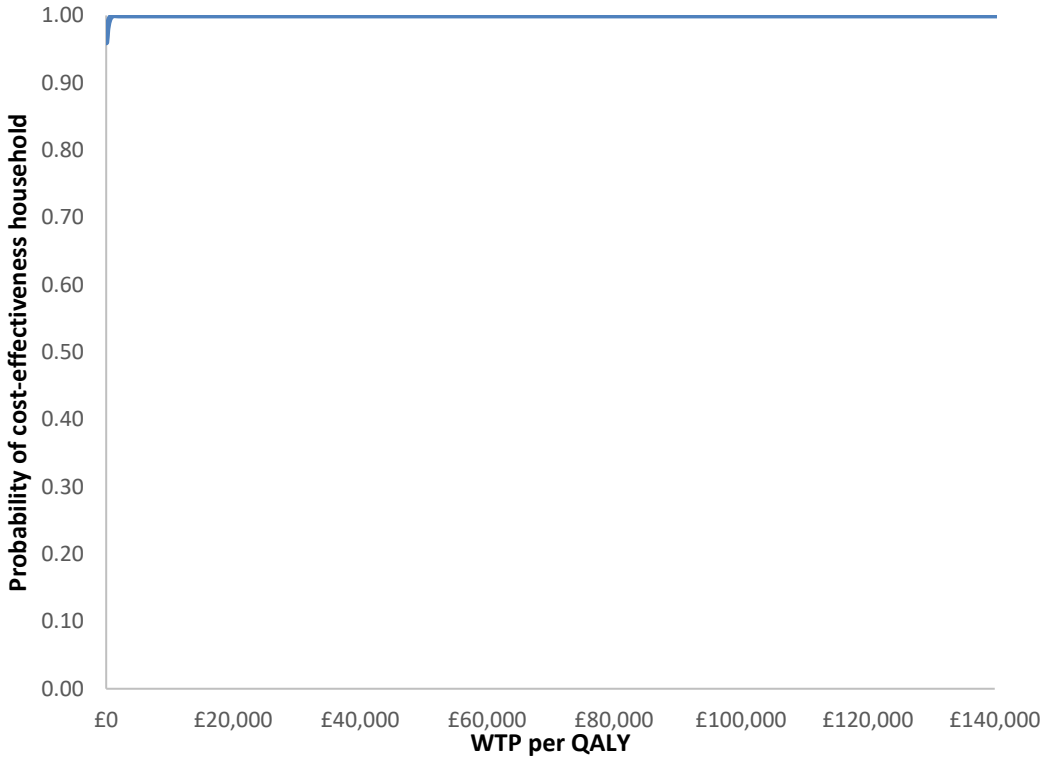


Figure 7.14: Household lifetime CEAC for the SFH12m base-case

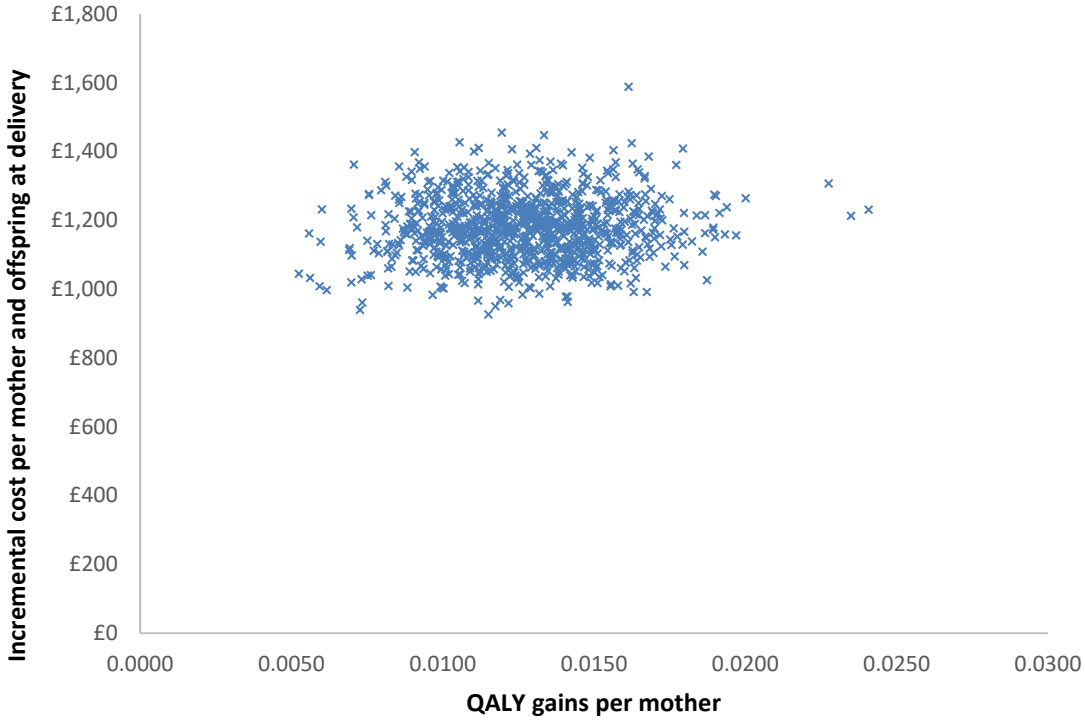


Figure 7.15: Scatterplot for incremental costs and QALY gains expected from RSDP base-case within pregnancy analysis

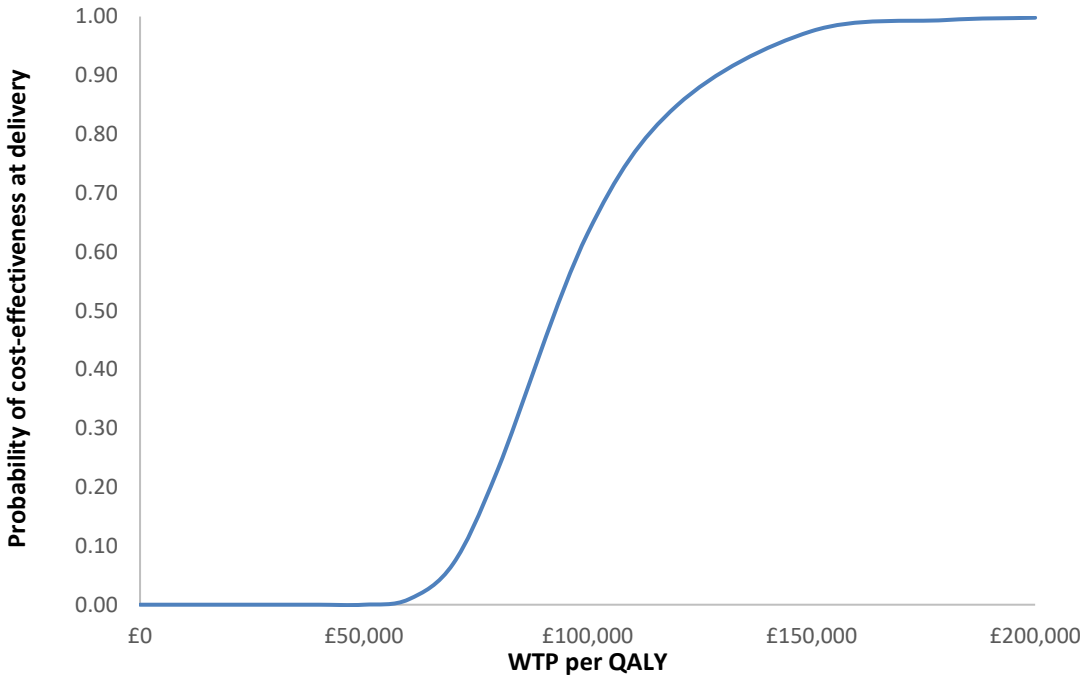


Figure 7.16: CEAC at delivery for the RSDP base-case

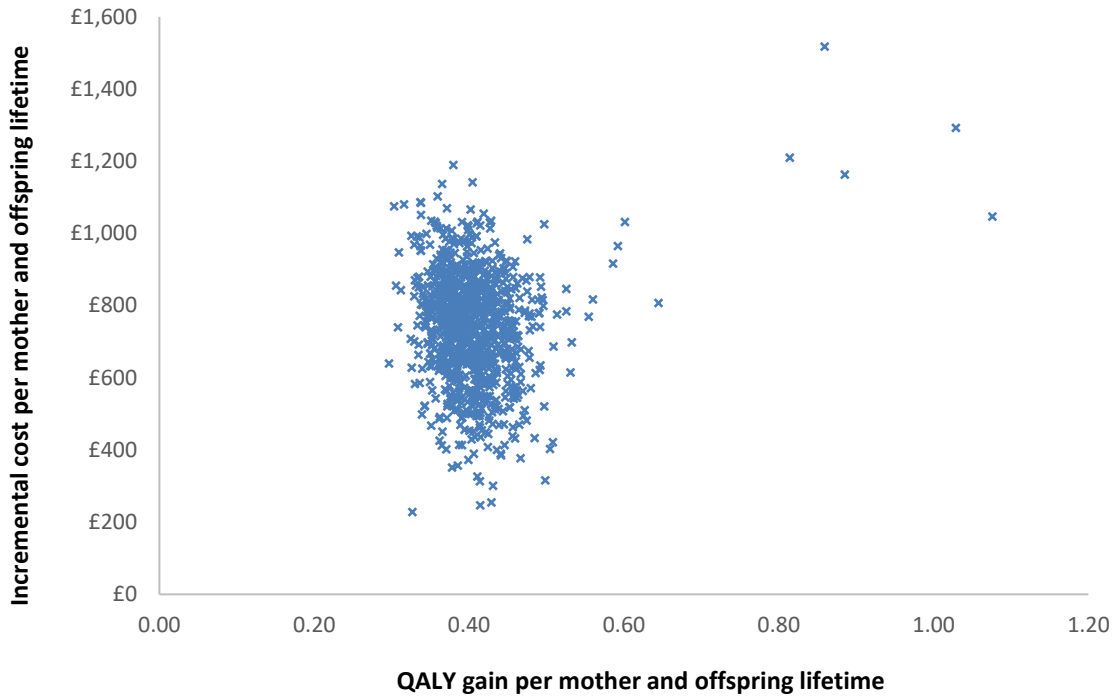


Figure 7.17: Scatterplot for incremental costs and QALY gains expected from RSDP base-case mother and offspring lifetime analysis

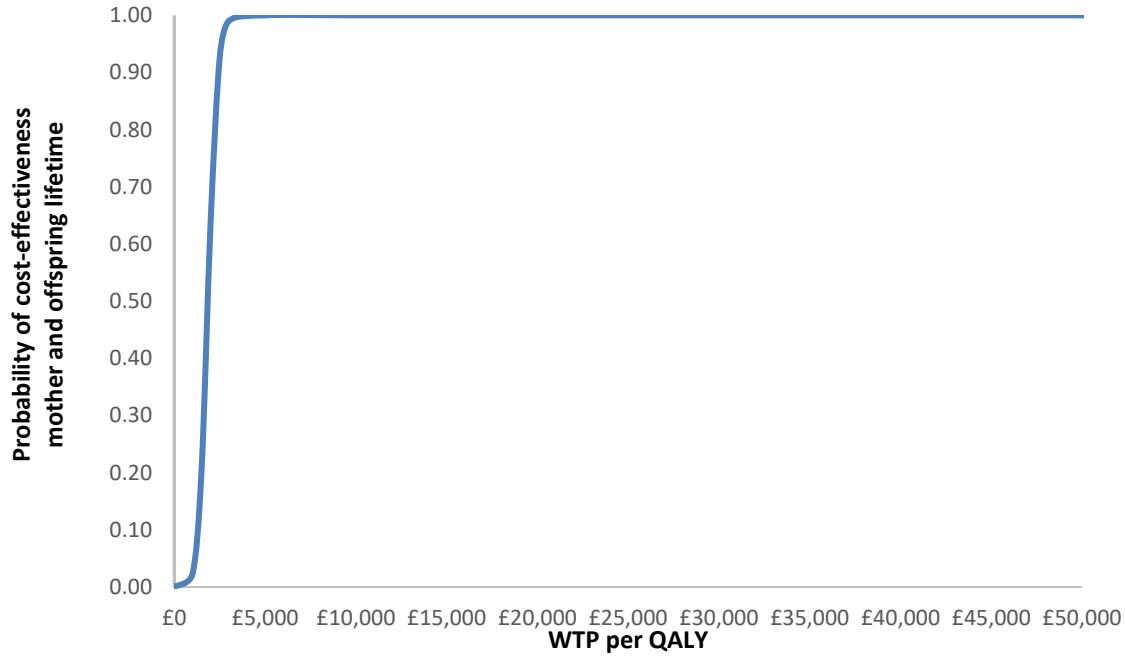


Figure 7.18: Mother and offspring lifetime CEAC for the RSDP base-case

The incremental cost and QALY gain estimations and the cost-effectiveness probabilities at different WTP thresholds are demonstrated in Figures 7.19 to 7.34 for the cautious-case scenario. In keeping with the base-case analyses, in the within pregnancy analyses, all iterations fall into the north-east quadrant and show that interventions are not cost-effective at delivery with little uncertainty around the incremental cost and QALYs. In the mother and offspring analyses, some uncertainty is observed for both incremental QALY and cost estimations. In the household analyses, the majority of iterations fall into the south-east quadrant, suggesting SFH3m and SFH12m are dominant over the comparator. However, there is some probability that the interventions are not dominant but cost-effective.

The figures show that, in the lifetime estimations, the probability of cost-effectiveness is 100% at £30,000 per QALY threshold for all the interventions although at delivery it is 0%. The probability of cost-effectiveness reaches 100% around a WTP of £5,000 per QALY in the mother and offspring lifetime analyses for SFH3m and SFH12m cautious-case scenario. Similarly, 100% probability of cost-effectiveness is achieved at around £3,000 for RSDP. The household CEACs show that the interventions can be viewed as highly cost-effective. Even if the decision-maker is not willing to pay for QALY gains, the cost-effectiveness probability is 96% for SFH3m cautious-case (Figure 7.24), and 90% for SFH12m cautious-case (Figure 7.30).

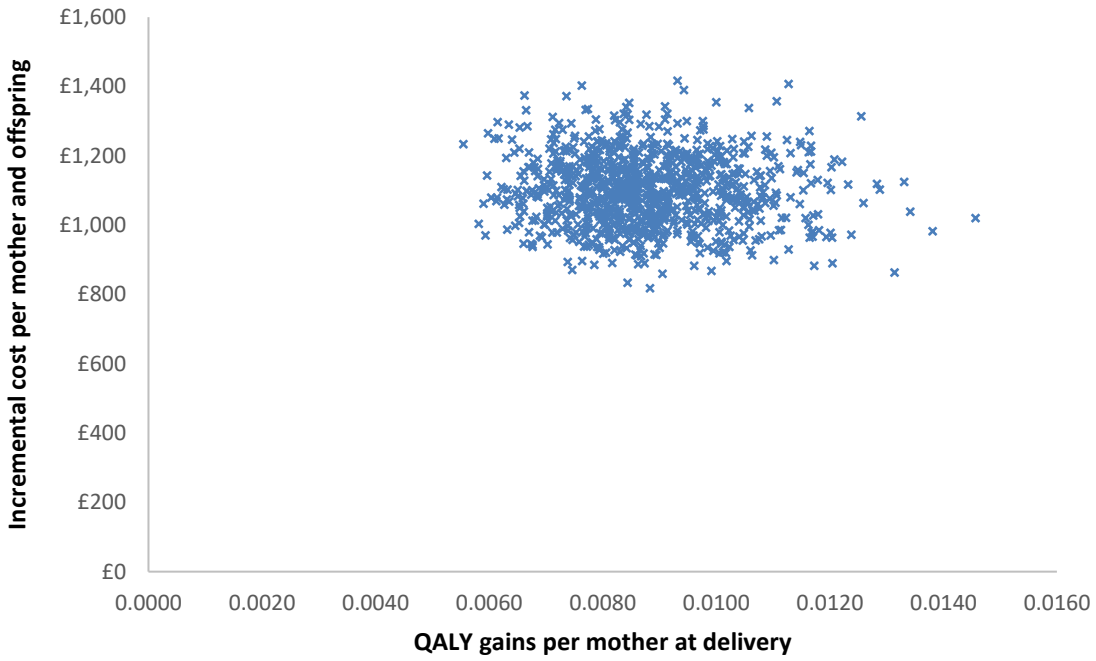


Figure 7.19: Scatterplot for incremental costs and QALY gains expected from the SFH3m cautious-case within pregnancy analysis

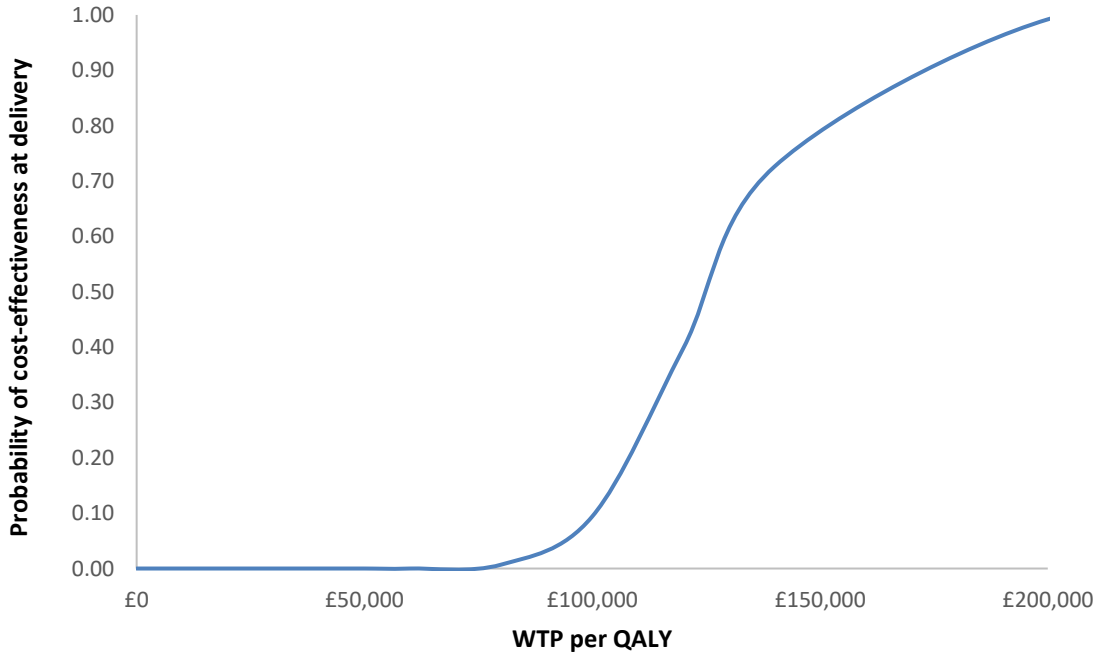


Figure 7.20: CEAC at delivery for SFH3m cautious-case

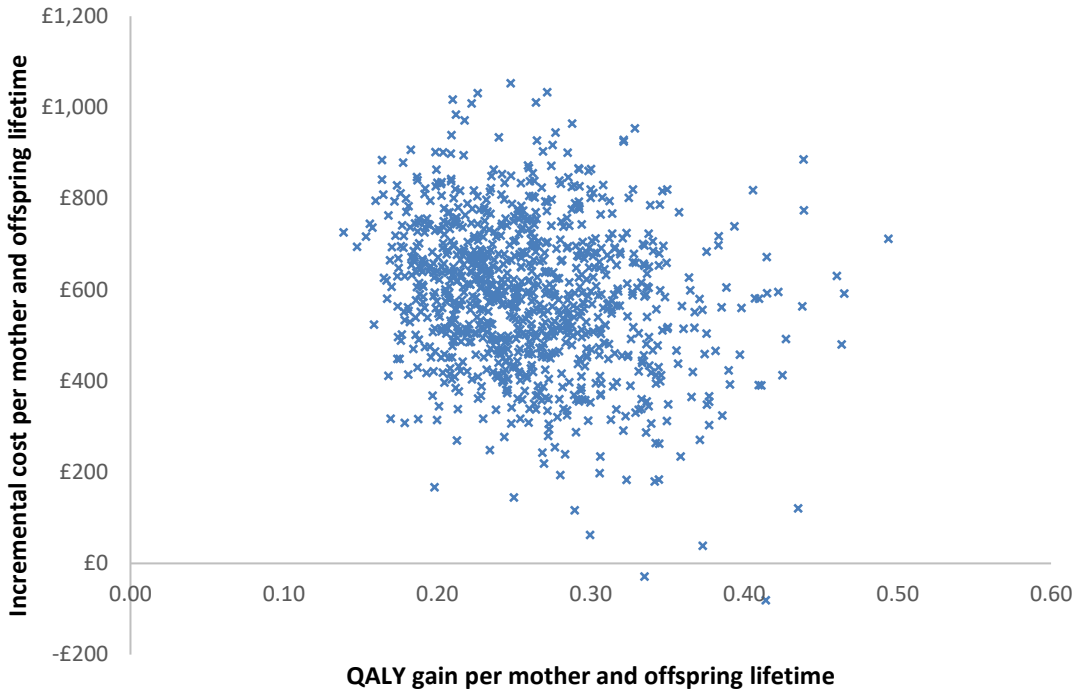


Figure 7.21: Scatterplot for incremental costs and QALY gains expected from the SFH3m cautious-case mother and offspring lifetime analysis

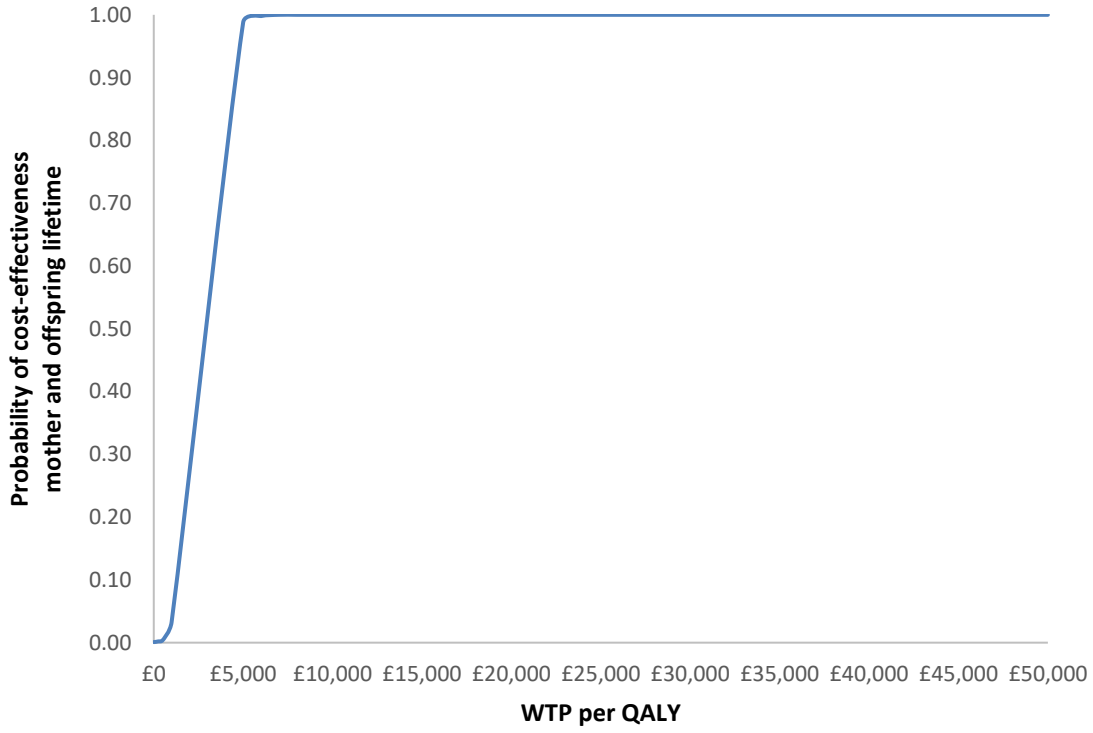


Figure 7.22: Mother and offspring lifetime CEAC for SFH3m cautious-case

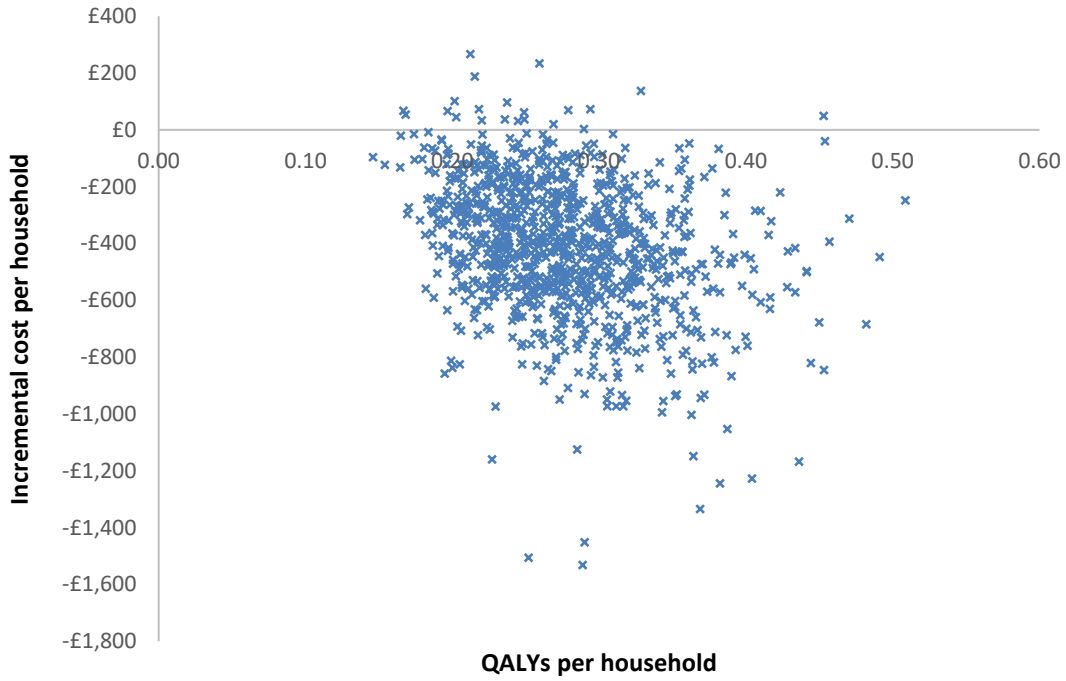


Figure 7.23: Scatterplot for incremental costs and QALY gains expected from the SFH3m cautious-case household analysis

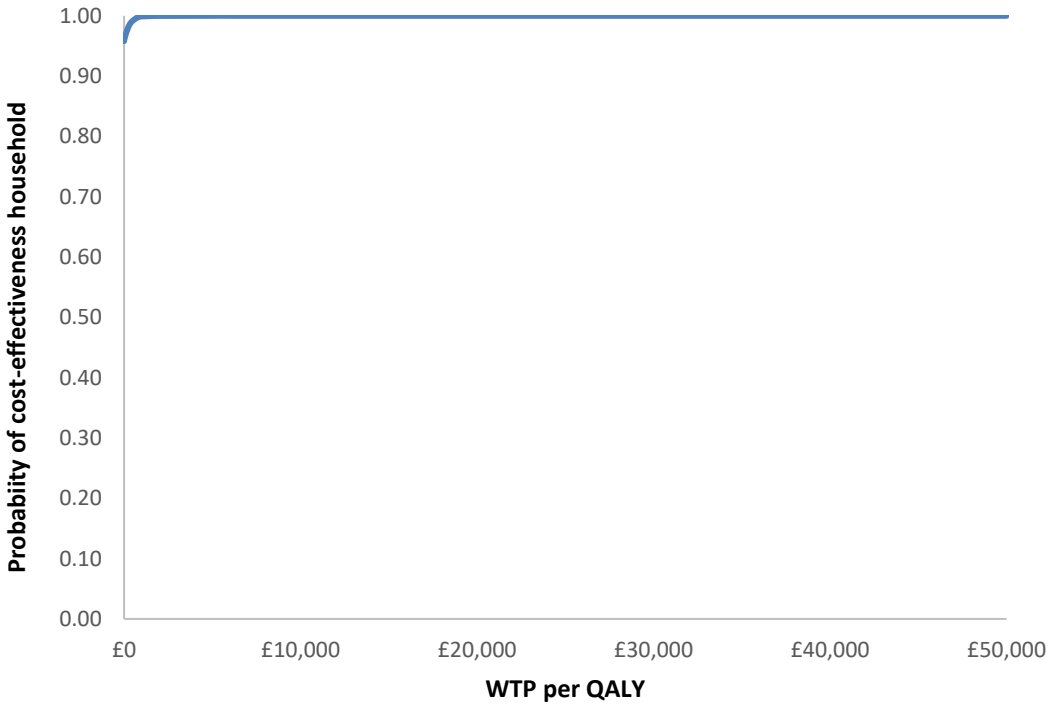


Figure 7.24: Household lifetime CEAC for SFH3m cautious-case

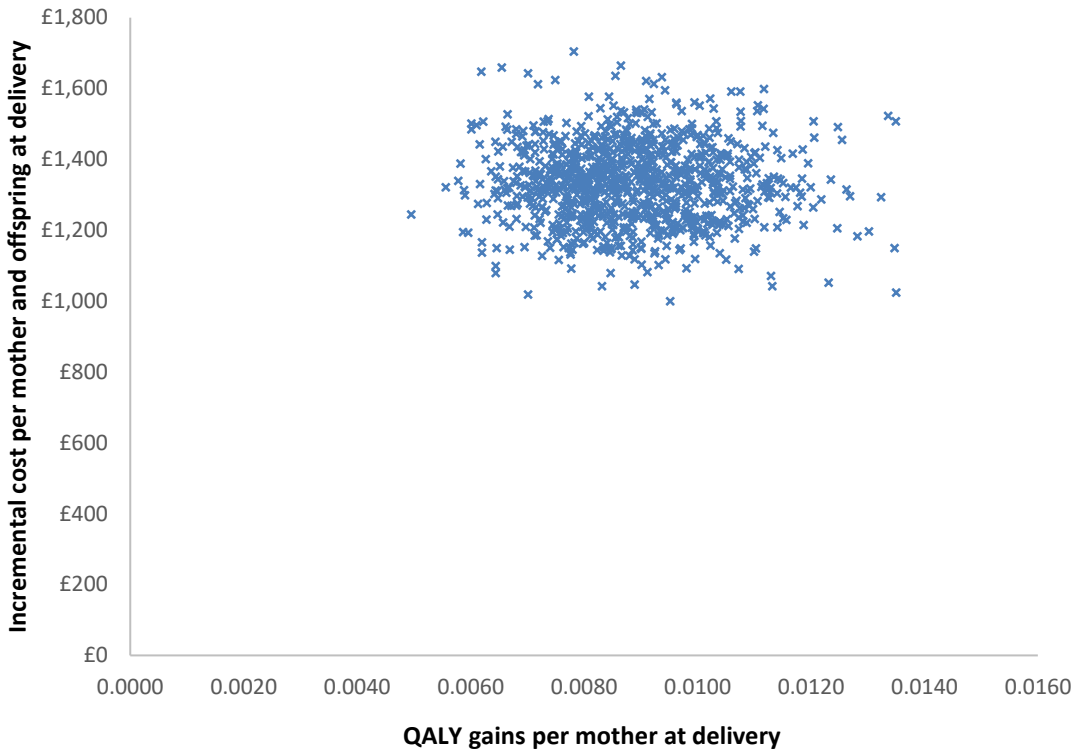


Figure 7.25: Scatterplot for incremental costs and QALY gains expected from the SFH12m cautious-case within pregnancy analysis

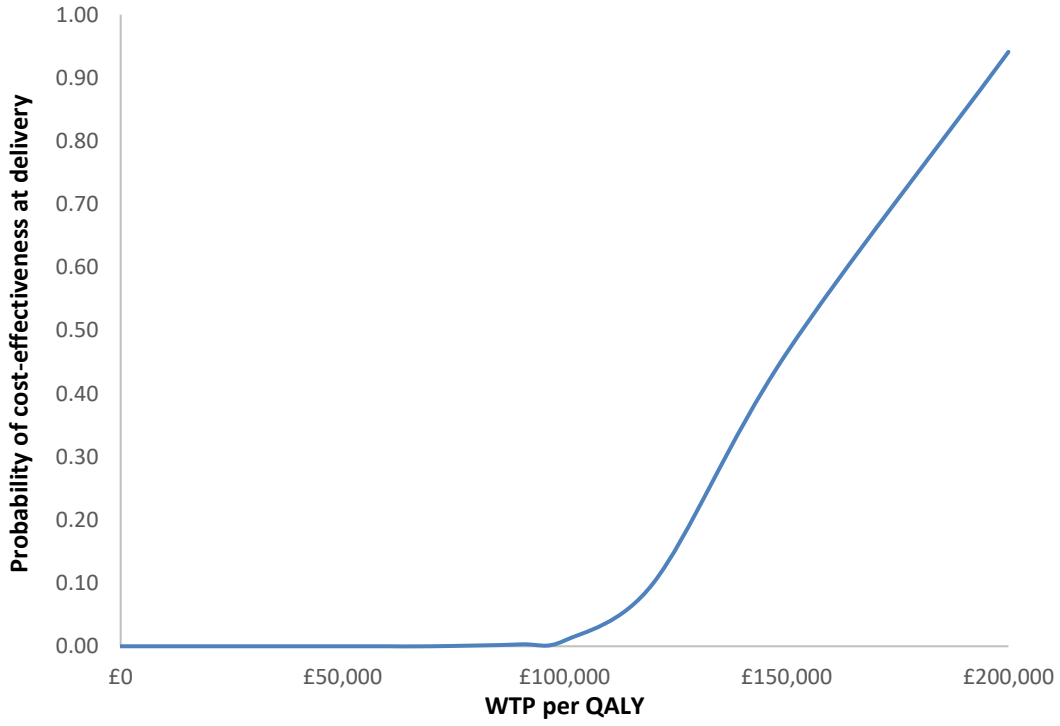


Figure 7.26: CEAC at delivery for SFH12m cautious-case

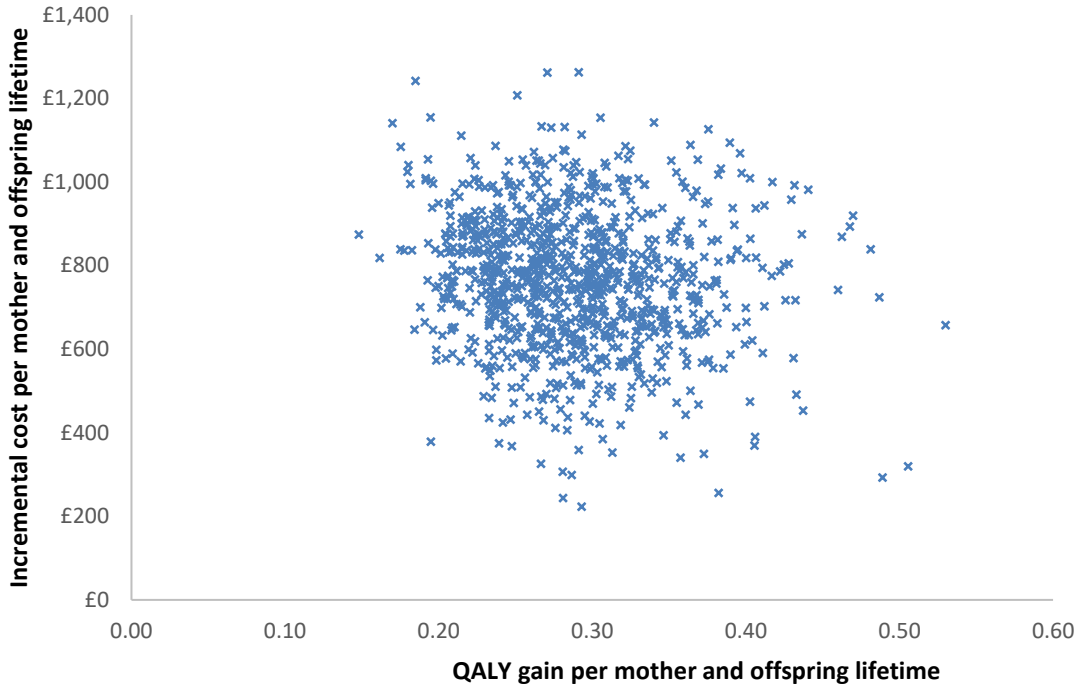


Figure 7.27: Scatterplot for incremental costs and QALY gains expected from the SFH12m cautious-case mother and offspring lifetime analysis

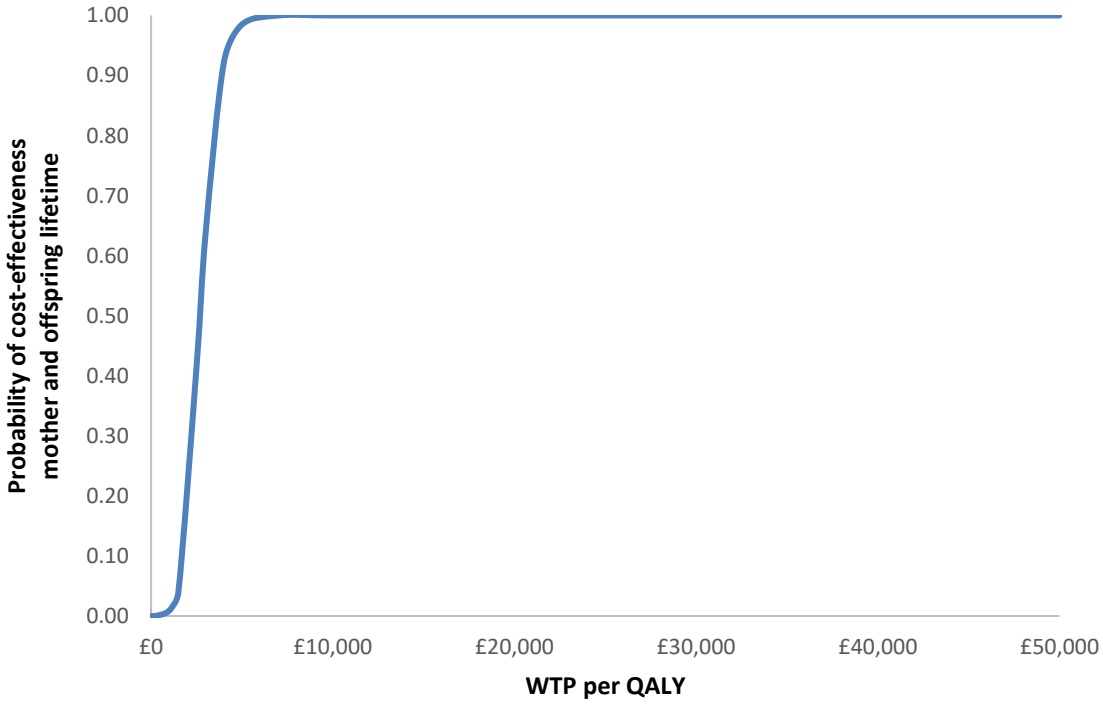


Figure 7.28: Mother and offspring lifetime CEAC for the SFH12m cautious-case

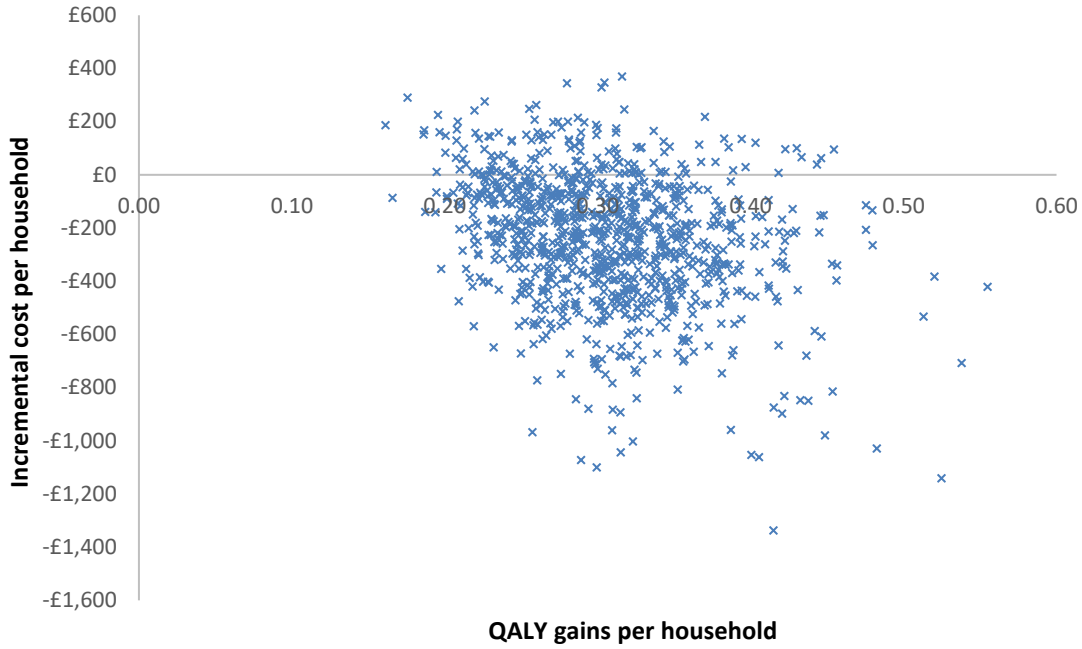


Figure 7.29: Scatterplot for incremental costs and QALY gains expected from the SFH12m cautious-case household analysis

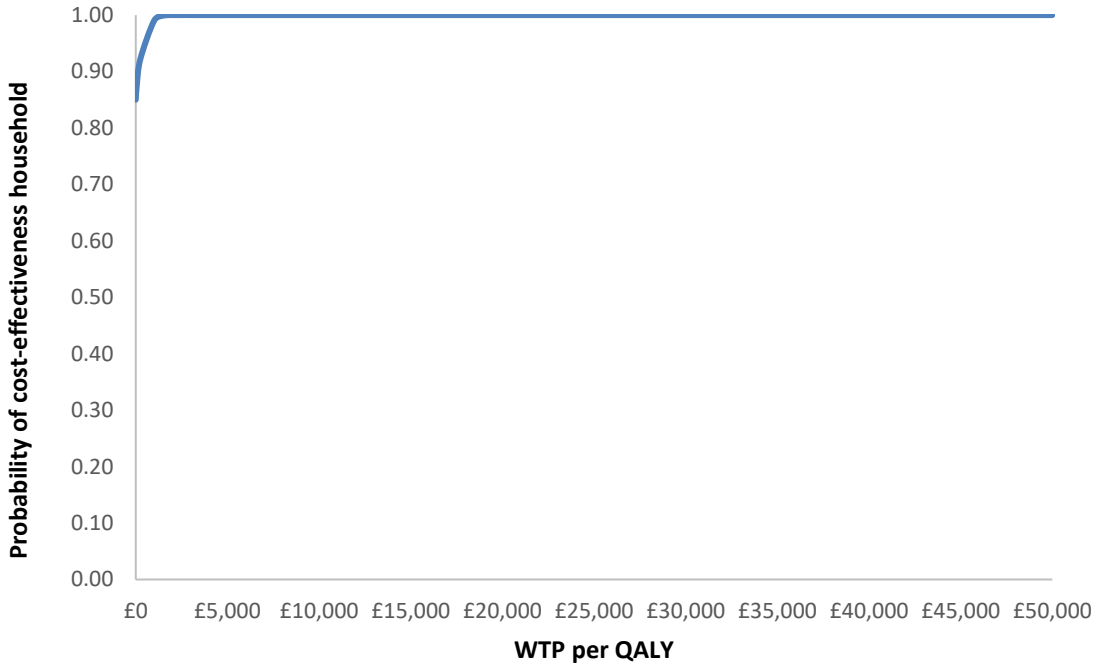


Figure 7.30: Household lifetime CEAC for the SFH12m cautious-case

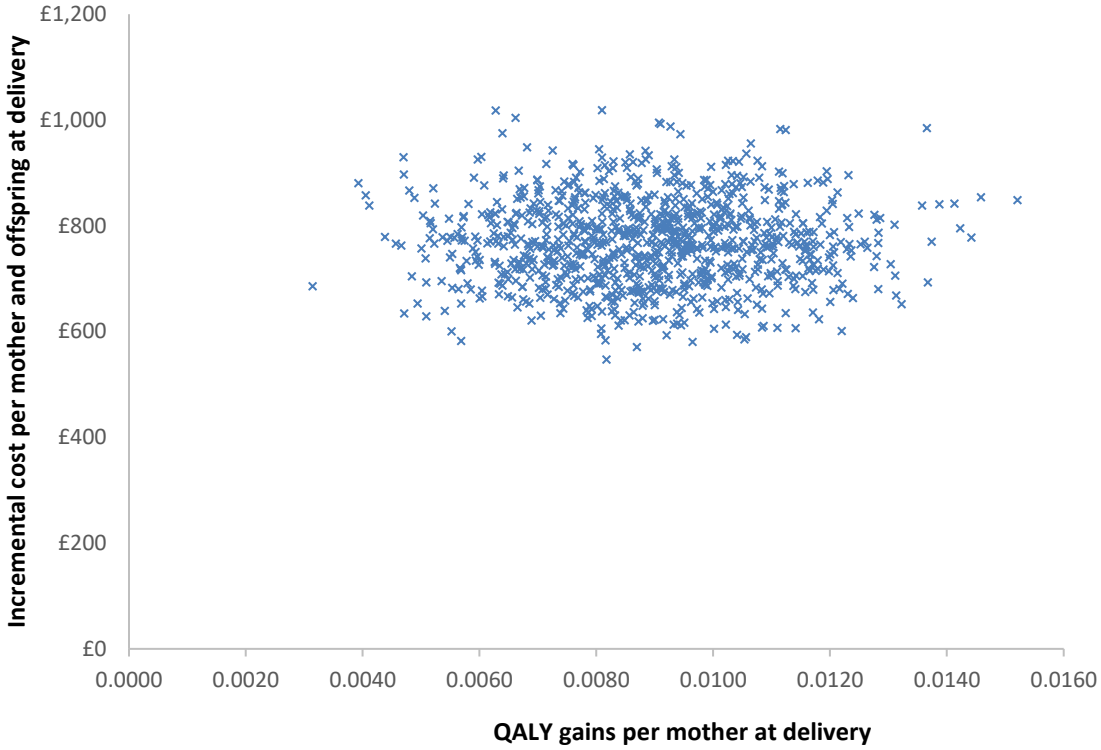


Figure 7.31: Scatterplot for incremental costs and QALY gains expected from the RSDP cautious-case within pregnancy analysis

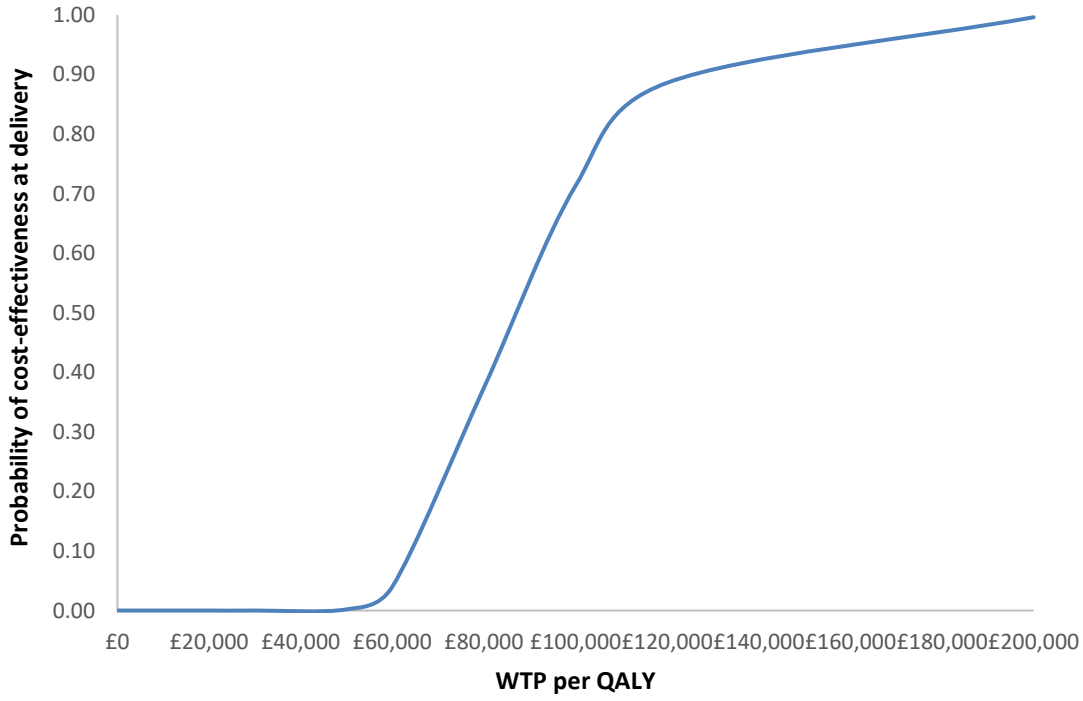


Figure 7.32: CEAC at delivery for the RSDP cautious-case

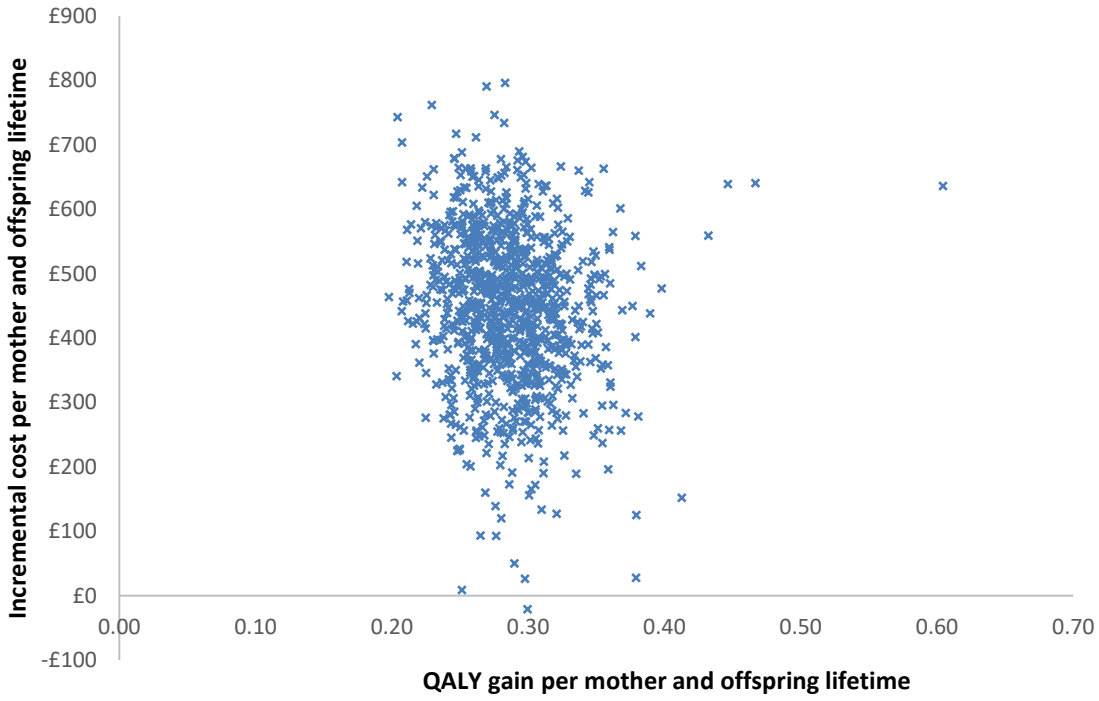


Figure 7.33: Scatterplot for incremental costs and QALY gains expected from the RSDP cautious-case mother and offspring lifetime analysis

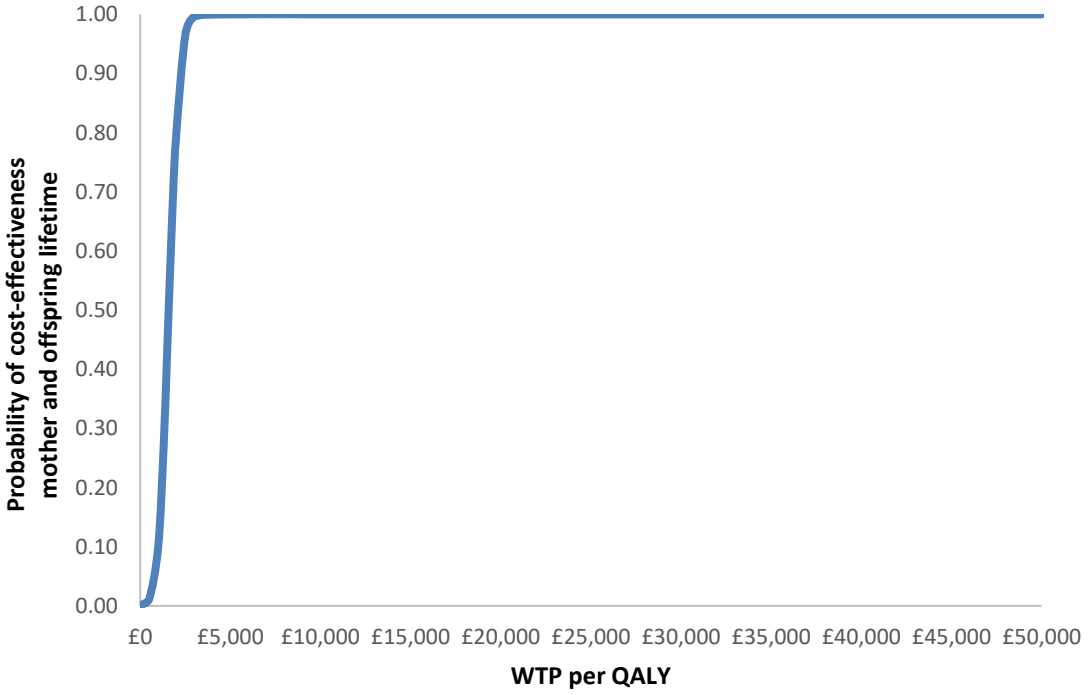


Figure 7.34: Mother and offspring lifetime CEAC for the RSDP cautious-case

7.5 DISCUSSION

This study evaluated hypothetical SDP interventions based on the characteristics identified in the literature, such as providing financial incentives and incorporating partners. Two cessation models (SFH3m and SFH12m) and one reduction in smoking during pregnancy model (RSDP) were assessed. The analysis indicates that long-term, intensive behavioural support alongside comparatively high financial incentives with a household approach would be a cost-effective way of helping pregnant smokers to quit and to assist those who are not ready to quit in reducing the number of cigarettes consumed.

7.5.1 Strengths and Limitations

This is the first economic evaluation of smoking cessation and reduction interventions for pregnant women which consist of long-term intense behavioural support with a household approach and financial incentives. The analyses show that, for a cohort of 1,000 smoking women, the hypothetical cessation interventions could generate 467 additional quitters amongst mothers and partners at delivery in the base scenario, and 286 additional quitters in the cautious scenario. Additionally, the hypothetical reduction intervention could help 730 women reduce smoking in the base scenario and 514 women in the cautious scenario.

The results show that piloting these interventions offers value, followed by a feasibility and applicability assessment. However, there some considerations around bio-

chemical verification of abstinence. Firstly, the precision of CO verification for assessing smoking reduction would pose a specific difficulty, especially if in households with another smoker. Additionally, the use of e-cigarettes requires attentions since this may impact on the precision of saliva cotinine testing. Moreover, the use of financial incentives may increase intervention engagement and lead to greater retention in the intervention arms, which may result in trial imbalance and confounding of results. Although, in the most recent UK trial, the proportion of lost to follow-up were similar in the incentives (15%) and control arms (14%), this is an important consideration for future studies (Tappin et al. 2015).

The study is not without limitations. Firstly, the effectiveness of the hypothetical interventions was calculated based on discrete trials of SDP interventions, and the combined impact of several characteristics (i.e. duration, partner support and high amount of financial incentives) might be different than those estimates. Moreover, the studies were conducted in Scotland and the USA not England. Thus, the effectiveness of such interventions might not be the same amongst women in England. The impact of those was mitigated by taking a conservative approach in the estimations and by conducting cautious scenario analyses.

The two trials that the effectiveness evidence based on were dated, and quit rates might be higher in those studies than the more recent ones due to the changes in the ingredients of cigarettes and also in the sensitivity of bio-chemical verification tools (Donatelle et al. 2000, McBride et al. 2004). Additionally, the impact of uptake and socioeconomic status on effectiveness was not considered in this study. Nonetheless,

this was an exploratory study to assess quit numbers, potential healthcare savings and cost-effectiveness of hypothetical optimum interventions designed based on the best available evidence.

To the best of the author's knowledge, this is the first study with an intervention designed specifically for pregnant smokers who are not ready to quit entirely. Thus, designing the reduction intervention was challenging due to the paucity of data. The only published intervention providing financial incentives for pregnant women who set a quit date and achieved reduction targets included drug-dependant women (Tuten et al. 2012). Hence, the impact of financial incentives on women who are not drug-dependant might be different. If they are more effective amongst drug-dependant women, then the study might be potentially overestimating the benefits of RSDP. In contrast, if they are less effective amongst that group the study would be underestimating the benefits of the intervention. Similarly, the cessation trials used in this study did not focus on "hard-to-reach" groups which may impact on generalisability in relation to such groups. Hence, research is needed to understand the effectiveness, acceptability, and feasibility of these interventions amongst hard-to-reach groups.

The ESIP.H model used to assess the interventions is the first economic model with a household approach which allows estimation of the spill-over effects of SDP interventions and the impacts of reducing smoking. However, the limitations arising from the model assumptions discussed in Chapter 5 should be considered when interpreting its outcomes.

An important assumption is that the interventions would not make any impact on quit rates one year after delivery among women who smoked during pregnancy, by assigning the same probabilities to the control and intervention groups. Since there are fewer smokers left in the intervention groups than in the control, the number of new quitters one year after delivery is higher in the control group and the gap in the number of quitters between the control and intervention groups is lower one year after delivery. Thus, the benefits of SDP interventions are potentially underestimated in this study.

7.5.2 Comparison with Previous Economic Evaluations

Previously, an economic evaluation of the CPIT study found that high levels of financial incentives provided until delivery were cost-effective (Boyd et al., 2016). The current study supports their findings and suggests that high intensity, long-term financial incentives interventions with a household approach could produce significant health benefits and be cost-effective when the impacts on the offspring and partner are considered.

To the best of the author's knowledge, there are no published economic evaluations of SDP interventions designed for pregnant women who are not committed to quit entirely.

7.5.3 Policy Implications

The SDP interventions published to date have limited impact on quit and abstinence rates and they are cost-effective mainly because the intervention costs are typically low (Jones et al., 2015). The current study suggests that there is a case for investing more resources in supporting women who smoke during pregnancy to quit, because of the comparatively high estimated quit rates and the cost-effectiveness evidence. For example, the hypothetical SFH3m and SFH12m base scenarios are estimated to generate additional 349 quitters amongst mothers at delivery per 1,000 participants (Tables 7.16 and 7.17), compared to only 35 in the MiQuit intervention (Table 6.5), that is approximately 10 times of the number of quitters generated with MiQuit. This also translates as producing 221 additional smoke-free houses per 1,000 smoking pregnant women compared to MiQuit that generates 69 (Tables 6.15 and 7.17). Furthermore, one year after delivery, the excess numbers of quitters are estimated as 143 for the SFH12m base scenario (Table 7.17) and three for MiQuit (Table 6.5).

According to the study outcomes, providing cessation support until three months postpartum (SFH3m) is more cost-effective than continuing the intervention to one year postpartum (SFH12m) due to the increased costs in the latter. However, SFH12m generates a higher number of quitters. Thus, spending more to achieve greater health outcomes could be considered by the decision-makers since both interventions are dominant over the comparator.

In addition to the provision of financial incentives, the optimum interventions proposed in this study include regular contact with midwives through the postpartum period rather than referral to Stop Smoking Services. That is in line with the "*continuity of carer*" imposed by the *"Better Births"* change plan for maternal care services (National Maternity Review, 2016). Additionally, maternal smoking at the time of delivery is one of the four components of CCG Improvement and Assessment Framework as part of the "*Better Births*" programme. Hence, it is hoped that this study would inform decision-makers while re-designing their services.

At present, only one quarter of pregnant smokers engage with the NHS SSS (NHS, 2018). By offering support to those not committed to quitting, healthcare providers can increase the reach of their services as well as achieving greater health benefits. The hypothetical RSDP intervention suggests that interventions aiming to reduce cigarette consumption during pregnancy also warrant attention, and thus support to reduce smoking for women who are not ready to give up should be part of the SDP programmes.

Moreover, considering high SDP rates amongst women from low socioeconomic backgrounds, these hypothetical interventions could help reduce the gap in health inequalities by supporting deprived households. Similarly, because non-smokers in the lowest income group are the most likely to be exposed to SHS (ONS, 2018b), having a household approach would have considerable impact on reducing SHS in addition to a decline in SDP rates.

7.6 CONCLUSION

Achieving the national ambition of 6% or less SDP requires provision of much more inclusive and intense help for expectant mothers and the ESIP.H model has the potential to help decision-makers design optimum interventions from a household perspective. The analyses suggest that long-term financial incentives interventions could offer significant health benefits as well as achieving the cost-effectiveness criteria.

7.7 CHAPTER SUMMARY

This chapter presented an economic evaluation aimed to identify the characteristics of hypothetical optimum SDP interventions. The optimum interventions were conceptualised based on the literature around SDP interventions and scenario analyses were undertaken by applying different effectiveness assumptions. Based on the current evidence, this study suggests that long-term financial incentives combined with a household approach could provide greater health benefits than the types of interventions that have been most widely used to date, and that they are likely to be cost-effective. The following chapter explores the use of high-income country based economic evidence on SDP interventions in low and middle-income countries.

CHAPTER 8: INFORMING HEALTH POLICY IN LOW AND MIDDLE INCOME COUNTRIES

8.1 INTRODUCTION

Since the economic analyses conducted in this thesis used UK-based data, it was important to understand the applicability of the findings in low and middle-income countries (LMIC). This chapter explores the challenges of using high income country (HIC)-originated health economic evidence in LMIC settings from the perspectives of informants working in an international public health organisation. Firstly, the background on SDP in LMICs and the transferability of health economic evidence is presented. Then, the case study is reported, followed by a discussion of the implications of its findings.

8.1.1 Smoking during Pregnancy in LMICs

At a regional level, the prevalence of SDP is at the highest in Europe (6%) and the lowest in Africa (1%) (Lange et al., 2018), yet, SDP is a significant health problem in many LMICs. A systematic review estimating the prevalence of SDP (Lange et al., 2018) showed that SDP is high in some middle-income countries (MICs), including Turkey (15%), Argentina (11%) and Jordan (9%). Additionally, in some LMICs where SDP prevalence is low, smokeless tobacco use is common, such as in India and Madagascar

where SDP prevalence is 1% and 0.4% respectively, whereas the prevalence of smokeless tobacco use in pregnancy is 7% and 12% respectively (Caleyachetty et al., 2014). Furthermore, smoking prevalence is increasing amongst women in LMICs and it is forecast to reach 20% in 2025 (Samet et al., 2001). This indicates a potential rise in SDP as well. Hence, tobacco use and SDP is a significant health problem in LMICs despite the varied magnitude across different settings.

The socioeconomics of SDP in LMICs is not well established because there are limited studies investigating the relationship between SDP and socioeconomic status. In the absence of sufficient data for SDP, smoking patterns in females could be an indicator of SDP rates. The socioeconomics of female smoking could be evaluated at two levels; the country level and individual level. Firstly, smoking patterns in LMICs vary based on the country income group. An analysis of the World Health Survey data comparing LICs and MICs shows that female smoking is lower in LICs and less affluent women with less education are more likely to smoke, but there is no such relationship in MICs (Hosseinpoor et al., 2012). Secondly, studies report different relationships between female smoking and individuals' socioeconomic status across MICs; in some countries (e.g. Albania and Moldova) increased education and improved wealth are related to greater risk of smoking for women although the opposite is the case for many MICs (Hosseinpoor et al., 2012, Sreeramareddy et al., 2018).

Additionally, limited studies on the socioeconomics of SDP in MICs report different findings based on setting. For example, in Turkey, SDP is reported to be more common amongst more educated women (Aslan et al., 2014), whereas in Cambodia, less

educated women tend to smoke during pregnancy (Singh et al., 2013). Therefore, in MICs, the correlation between socioeconomic status and SDP differs between countries; as a result the importance of SDP interventions in terms of reducing health inequalities across MICs varies too. There is very limited evidence about the socioeconomic determinants of SDP in LICs. One study reported no significant impact of literacy on any kind of tobacco use during pregnancy although second-hand smoking was more prevalent amongst those who were illiterate (Chomba et al., 2010).

Another related issue is the availability and accessibility of smoking cessation services for pregnant women in LMICs. There is no available data on this across countries. Nevertheless, the proportion of women who smoke daily and quit just before or during pregnancy gives an indication. Although the overall proportion of women who smoke during pregnancy is lower in LMICs compared to HICs, a greater proportion of smoking women in LMICs continue to smoke during pregnancy (e.g. 80% in Western Pacific) compared to those in HICs (e.g. 30% in Europe) (Lange et al., 2018). This could be partly attributable to the fact that smoking pregnant women in LMICs have limited or no access to cessation support.

8.1.2 Transferability of Health Economic Evidence on SDP Interventions from HICs to LMICs

A range of SDP interventions have been found to be effective and cost-effective in HICs (Cahill et al., 2013, Taylor, 2009, Chamberlain et al., 2017). However, little evidence exists about their cost-effectiveness in LMICs. A systematic review of smoking

cessation interventions for adult smokers in LMICs reported six studies assessing the cost-effectiveness of such interventions in LMICs (Owotomo, 2016). These interventions included physician advice and pharmacotherapy but there was no evaluation of psychosocial interventions (e.g. social support, incentives). Similarly, the review by Chamberlain (2017) found only one psychosocial intervention conducted in four South American countries, which did not include an economic evaluation (Belizán et al., 1995). Therefore, decision-makers in LMICs need to rely on evidence from HICs, as is the case for many other public health issues (Drummond et al., 2016).

There are some guidelines for transferring economic evaluations across jurisdictions (Barbieri et al., 2010, Boulenger et al., 2005, Drummond et al., 2009, Drummond et al., 2016, Goeree et al., 2011, Knies et al., 2010, Nixon et al., 2009, Reinhold et al., 2010, Welte et al., 2004). These guidelines provide guidance for the transferability of economic evidence, mostly focusing on the technical issues including baseline data, treatment effect and unit costs. Some other factors in addition to the methodological issues, such as patient and healthcare characteristics have been identified as important in one systematic review (Goeree et al., 2007). Yet, most of the studies included in that review focused on transferring evidence across high-income settings.

A study by (Drummond et al., 2016) concludes that use of such guidelines is very limited in MICs and the most important reasons are the different practice patterns and the availability of facilities. This indicates issues other than transferability in terms of technical aspects. However, most transferability guidelines do not investigate wider issues that would inhibit the applicability of health economic evidence. For example,

LMIC settings are very different to HICs not only in terms of healthcare systems but also in terms of priorities and the characteristics of female smoking. Similar limitations exist in the frameworks for priority setting in LMICs using health economic evidence. For instance, less than half of the frameworks consider the impact of equity and feasibility (Wiseman et al., 2016). Furthermore, very few studies have focussed on a particular health area or condition to analyse the challenges and opportunities associated with using such evidence in LMICs. To the best of the author's knowledge, there is no published guideline or framework with a specific focus on SDP or smoking amongst women. Hence, the existing frameworks are not sufficient to explain the applicability of HIC-based economic evidence on SDP in LMICs.

8.2 METHODS

8.2.1 Objective

This case study aimed to explore the potential use of HIC-based economic evidence on SDP interventions to influence health policies in LMICs by interviewing expert informants from an international public health organisation (IPHO).

8.2.2 Setting

The IPHO where this research was conducted is a leading global organisation which aims to influence health policies at international and national level by providing leadership and technical support. There is a department based at its headquarters,

which focuses on tobacco control and cessation policies and provides recommendations on tobacco-related issues to influence policy-making in LMICs as well as in HICs.

Across the world, the IPHO has six regional offices which accommodate regional tobacco officers. They provide guidance to national authorities to comply with the IPHO recommendations. They collaborate with the IPHO staff at the headquarters and country offices and external experts for assessments, implementation and providing guidance to ministries. Regional offices form the bridge between the headquarters and country offices. The country offices work in close collaboration with national tobacco control programme directors, referred to as country focal points.

Apart from providing international recommendations, there are three main ways the IPHO could get involved with health policy-making processes at the national level:

- The IPHO proactively approaches particular countries if funding is available,
- Regional offices can approach countries if they have their own sponsors,
- Governments can approach the IPHO for help (sometimes with their own funds).

The department works closely with officers who are based in the regional or country offices to implement tobacco control policies. This department provides a unique opportunity to access the global expertise on smoking cessation. Hence, this specific organisation was chosen as the setting of the case study.

8.2.3 Sampling

Purposeful sampling was used to identify key people with the expertise to provide information on the issue. The director and the senior cessation specialist of the department for tobacco policies and cessation were approached as the "key informants". Additionally, the snowballing approach, which can be defined as recruiting new participants based on the suggestions of existing participants, was followed to identify the informants (Noy, 2008). Overall 18 informants who were knowledgeable about the issue and had experience of working in LMICs were named, including regional officers, public health experts and health economists. LMICs were identified based on the classification by World Bank (2018).

Among the regional officers, three agreed to participate while the regional officer for Europe declined on the grounds of not having sufficient expertise in tobacco cessation. The regional officer for South America suggested the previous regional officer because they were more knowledgeable on cessation; hence the previous officer was invited and participated. Similarly, the previous regional officer for Africa, who worked in the IPHO between 2010 and 2017, agreed to participate. Therefore, five of the six regions were represented by attendees who served as regional officers and had extensive information about their regions. Although the regional officer for Europe was not able to attend, some informants from the headquarters, especially the senior cessation specialist and all regional officers, provided information about some European countries.

Some country officers and country focal points (n=9) were invited based on suggestions of the regional officers, and seven individuals responded to the invitation. Two of the country officers (Jordan, Uruguay) suggested that their focal points working closely with the IPHO (i.e. Head of the National Tobacco Control Programme) would be more knowledgeable on the issue than the country officers themselves, and they were invited to take part in the research. Similarly, the focal point for Iran was suggested by the regional officer for Middle East (who also participated in the study) because of having a good tobacco control system in place; and they agreed to participate.

The regional officer for South America suggested two experts from Uruguay and Argentina due to the high prevalence of SDP in those settings. Although those countries were classified as HICs according to the updated definition of the World Bank at the time of recruitment, their GDPs per capita are much lower than most HICs (e.g. UK) and they were MICs while implementing their initial tobacco control policies. Therefore, exploring their progress was deemed to be important, and they were included in the study.

Overall, 25 people were invited and 18 participated in the interviews. In qualitative studies, mostly there is no pre-defined sample size but the researcher aims for saturation (Saunders et al., 2018). Since the study was designed as a case study, a strategic approach was adopted, and the objective was to reach every expert available.

8.2.4 Data Collection

A topic guide was prepared for the interviews based on the literature and following discussions with the research team. The guide was then further developed by consulting the senior cessation specialist working in the head office prior to the interviews. Semi-structured interviews were undertaken with informants face-to-face, via video-calls, and phone-calls, depending on where the informants were based. Semi-structured interviews were preferred to be able to gain comparable data and due to the low possibility of interviewing one informant more than once (Bernard, 2018). The interviews were conducted between June 2018 and March 2019 and took on average 45 minutes. Fifteen interviews were audio-taped and three were recorded by note-taking at the request of the interviewees. A confidentiality agreement was signed by all parties before the interview. All recordings were transcribed in full.

An interpreter was employed during one interview because one informant did not speak English, following the recommendations for cross-language qualitative research (Squires, 2009). The interpreter was a bilingual senior health economist. The researcher and interviewer discussed the scope of the interview prior to the interview.

8.2.5 Ethical Considerations

The ethical approval for this study was granted by the University of Birmingham Ethics Committee (ERN_18-0626) and the Office of Compliance, Risk Management and Ethics

at the IPHO where the interviews were conducted. As required by the ethics team of the IPHO, the name of the organisation will not be disclosed.

Additionally, this study was conducted in accordance with the principles of the Declaration of Helsinki (Word Medical Association, 2013). All informants received an information letter explaining the objectives of the research and their written consents were obtained prior to the interviews. It was clearly stated that the informant was free to withdraw from the study at any time for any reason.

The study complied with the Data Protection Act and the collected data have been only available to the researchers to maintain the informant confidentiality. Any information which might have caused the identities of the informants to be disclosed (i.e. specific personal information which indicates one individual) was excluded from the analysis.

8.3 ANALYSIS

Although using qualitative methods in health economics studies is uncommon, different types of qualitative research have been conducted to enhance or interpret the quantitative research (Coast, 2017). Framework analysis (Ritchie and Spencer, 1994) was used for this research because it has an applicable, systematic structure and provides flexibility while interpreting data. There are previous studies using framework analysis in order to explain economic phenomena (De Allegri, 2017, Martinez-Alverez, 2017). The analysis followed five key steps (Ritchie and Spencer, 1994):

- Familiarising with the data by listening to the recordings, transcribing and reading the transcriptions,
- A framework was developed based on the initial interviews,
- Data were indexed using that framework, generating some codes,
- Charting was done by summarising the data informant by informant on an excel file,
- The data was analysed and interpreted based on themes. Reliability and rigour were ensured through independent coding and interpretation of the data by two researchers, followed by discussions.

8.4 RESULTS

8.4.1 Informants

The informants were working at different positions and had the experience of working in different parts of the world, enabling the research to cover a large geographical area. Table 8.1 below shows the informants' roles; the regions and countries on which the interviews focussed. The cessation specialist is the focal point in the organisation, working closely with regional and country offices to support them in establishing or improving their tobacco cessation services. The cessation specialist also provides training to the healthcare professionals in different countries. The regional officers are very knowledgeable about the countries in their specific regions.

All regional officers had at least five years of experience in their regional position, and most held a higher degree in public health. The other informants had at least 10 years

of experience in tobacco control. Two informants (I.8 and I.10) were not working in the tobacco department but in the maternal health department at the head office. Therefore, all informants were highly experienced.

Table 8.1: Roles and regions of the informants

	Role at the time of research	Region	No
Head office	Health economist	South America	I.1
	Health economist	LMICs in general	I.3
	Cessation specialist	HICs & LMICs	I.4
	Health economist	LMICs in general	I.5
	Technical officer	Africa	I.8
	Technical officer	Africa	I.10
Regional offices	Regional officer	Pacific	I.2
	Regional officer	Middle East	I.7
	Regional officer	South Asia	I.9
	Previous regional officer	South America	I.15
	Previous regional officer	Africa	I.17
Country offices	Country officer	Pacific	I.6
	Country focal point	Middle East	I.11
	Country officer	Europe	I.12
	Country focal point	Middle East	I.13
	Country officer	South Asia	I.14
	Country focal point	South America	I.16
	Country officer	South America	I.18

8.4.2 Key Themes

The analysis of interview data identified four key themes and associated sub-themes (Table 8.2). The first theme was the policy context which included the different characteristics of SDP in LMICs and the priority of cessation interventions aimed at expectant mothers. The second theme was about the characteristics of healthcare systems, covering limited resources and availability of data. The interviews also

provided useful information regarding the third theme; characteristics of potentially cost-effective interventions. The final theme focused on the use of economic evidence in LMICs relating to tobacco use during pregnancy. Those themes are explained in detail in the sections below:

Table 8.2: Key themes and sub-themes identified based on the interviews

Key themes	Sub-themes
Policy context	• Characteristics of SDP • Prioritisation of cessation interventions for pregnant women
Characteristics of healthcare systems	• Healthcare resources • Data availability • Access to cessation services
Potentially cost-effective interventions	• Service provision • Cocoon cessation • Social support • Financial incentives • Long-term support
Using economic evidence for policy-making in LMICs	• Country-specific evidence • Policy-making

8.4.2.1 Policy context

This theme involved policy-related issues, including the setting-specific characteristics of SDP that would impact on the use of HIC-based economic evaluations and the prioritisation of SDP interventions in the LMICs.

8.4.2.1.1 Characteristics of SDP

Most informants stated that SDP in many LMICs was not as common as in Europe, and only some LMICs (e.g. Bulgaria, South Africa) had a high level of SDP. However, some informants (I. 8, I.13 & I.17) emphasised that data on the prevalence of smoking was

not very accurate especially in some countries due to cultural norms which view women who smoke negatively. Therefore, the number of pregnant women who smoke or use tobacco products might be underestimated in some countries.

"In Muslim countries, like, I have been to Senegal, Mali, you know, the religion plays an important role and you will find that people are not keen to show they are smoking… They are underestimated actually because people tend to hide because of the cultural and religious setting." (I.8).

"*we did not ending up publishing that material but we started the process of tobacco cessation programmes in some countries. And to all the countries we went the demand for tobacco cessation when you compare males and females who come it was just about half for example in one country we found that of the people who are coming one third were women. So, the demand for cessation is a pointer to the fact that there may be some hidden figures amongst women.*"(I.17)

Additionally, although the prevalence of SDP was reported as low in many LMICs, the informants stated that many pregnant women used other tobacco products (e.g. chewing, shisha) to deal with pregnancy sickness. For example, one informant from the Middle East reported that although smoking in women was reported as under one percent, traditionally every household had waterpipes (shishas) and women used them too (I.11). Similarly, chewing tobacco was stated to be very common in India despite low levels of SDP (I.9). Thus, in such regions, the focus of an economic evaluation should be any kind of tobacco use not just smoking.

"So, basically, you know for my region it is always tobacco cessation not just smoking cessation because many women do not smoke but they chew tobacco due to being unable to afford cigarettes."(I.9).

Regarding the socioeconomics of SDP, the informants were asked about the study results showing that in some LMICs, high income and education was associated with increased risk of smoking amongst women (Sreeramareddy et al., 2018). Some informants linked this to the impact of education on distancing from cultural norms and exposure to the media (I.8). On the other hand, one of the informants from the Middle East was critical of those findings because of unintended sampling bias; women from disadvantaged backgrounds may not be participating in such surveys or they may not disclose that they smoke because of the cultural unacceptability of smoking for women (I.13).

"I would question that in one way; with increasing income the person moves into a higher socioeconomic standard where it becomes more acceptable to announce that you smoke, you drink that you live on your own. So, they would announce it much more easily, so they would respond to the surveys positively while the women from the lower socioeconomic backgrounds would stillbirth hide the fact that they smoke" (I. 13).

In addition, the informants from South Asia and the Middle East (I.9 and I.11) acknowledged there is a difference in the type of tobacco product consumed based on education and wealth, stating that smokeless tobacco products (e.g. shisha and chewing) are more common among less educated women, whereas cigarette smoking

is more common among more educated women. Related to that, wording in tobacco surveys was highlighted as well, as the verb "drinking" is used when referring to waterpipe use (I.13).

"*… If you ask someone 'Do you smoke?' people immediately respond like 'No, I don't smoke cigarettes'. The term for waterpipe is 'drink waterpipe'*." (I.13)

Another point linked to the socioeconomic status related to the general education level in LMICs compared to HICs; the informant from India (I.9) suggested that implementing cessation interventions would be easier in HICs because of the higher education level in the general population.

"…people are more educated in HICs so implementing these interventions is easier but here especially if you are focussing on chewing tobacco it is challenging because women who chew tobacco are not educated or have lower education" (I. 9).

8.4.2.1.2 Prioritisation of cessation interventions for pregnant women

Prioritisation of cessation interventions was identified as a key factor since the respondents acknowledged that SDP was not a priority in most countries (I.2 & I.7). In LMICs, the prevalence of SDP, limited resources, many competing health problems and the preference of tobacco control to cessation interventions were the key challenges mentioned in terms of prioritising SDP interventions.

"*Countries are doing their minimum for cessation services*" (I.7).

Political will was cited as a prerequisite for prioritising cessation interventions. Rwanda, Iran, Jordan, Turkey and Uruguay were mentioned as countries with political will to tackle tobacco use. Among HICs, Australia, UK and Sweden were named as good examples of significant political and practical endeavours.

"*I come from a country where the leader is really, you know, pushes for… there is strong will about this. They can easily implement these interventions only because they believe in these. They really give support to it and provide all necessary input for implementing this. So, leadership is critical. But, of course, you need time, time and strong leaders. And political will"* (I.8).

One of the informants from Africa mentioned the potential impact of cultural norms on the disinterest of policy-makers in tobacco use during pregnancy.

"The political infrastructure does not like to have these facts pointed at; that women are smoking, women are drinking alcohol, women want services for tobacco cessation."(I.17).

All informants believed that in a country with a strong tobacco control policy, it would be easier to develop and implement cessation interventions for pregnant women than where such policies were absent. They acknowledged that many LMICs did not have tobacco control policies in place (I.1, I.2 & I.7). The influence of tobacco companies was highlighted as one of the reasons for that (I.8). In parallel to not having tobacco policies, most LMICs did not have any smoking cessation services available at all (I.9).

Another related issue was the dominance of tobacco control interventions over cessation interventions. The informants acknowledged that in both HICs and LMICs, policy-makers were not convinced that cessation would be as effective as tobacco control interventions.

"For example, country […] increased tobacco tax almost 70% in one and a half year but did not improve cessation at all. I spoke to their ministry of health and the IPHO office there and the main reason is that decision-makers do not believe cessation really works. They do not want to invest in cessation policies because they seem to be costly and the result is not as clear according to them. However, tax increase itself does not solve the problem because you have illicit trade problem which makes tax policies more expensive" (I.1).

Not just at national level but also at the international level, more attention has been paid on tobacco control than cessation. One expert emphasised this by saying "… *you see, even in our department, we have five economists but one cessation specialist*" (I.3). Moreover, major donors of this IPHO have been more interested in tobacco control, and reluctant to invest in cessation interventions.

"The donors do not want to invest in this. People want to quit but we do not provide help for them. Where can they go? That is my question…" (I.6).

8.4.2.2 Characteristics of healthcare systems

The second theme was about the issues related to existing healthcare systems in LMICs. This included healthcare resources, data availability and access to cessation services.

8.4.2.2.1 Healthcare resources

One of the key issues highlighted by the informants was limited resources in LMICs. Finding financial support for a cessation intervention focusing solely on pregnant smokers was one of the key challenges raised by almost all the experts, not just due to the low prevalence of SDP but also because short-term benefits would not be so apparent compared to some other health interventions for TB or AIDS. For example, two informants (I.2 & 6) from the Pacific region stated that although SDP is often mentioned as a priority in the region, when it comes to funding it is not prioritised.

"…the political will is there but there is often blockage around following it through a plan and putting that on to a budget" (I.2).

Another related issue is a lack of trained healthcare professionals. In rural areas, primary care and most of other healthcare services are often provided by one physician and a nurse, and they have limited capacity to talk about smoking (I.2 & 4). Furthermore, healthcare professionals often are not trained in smoking cessation.

"Majority of the health providers are not trained or they are not confident to talk about this. They are very confident to talk about other issues like pregnancy-related issues but

they may not feel confident to do the counselling or talking about behavioural change" (I.4).

Additionally, the lack of national guidelines for smoking cessation services in most African countries was highlighted by two informants (I.8 and I.17).

"…standardised guidelines; many countries don't have them. In fact the majority don't have. To the best of my knowledge, the only countries which have those guidelines are Mauritius, Kenya, Gambia, Ghana and South Africa; so only these five countries. They have standardised guidelines."(I.17).

Moreover, one of the informants from South Asia (I.14) stated that many women in rural areas only speak their local language, which means all materials need to be prepared in local languages and translators would be required for counselling. Similarly, it was reported that some women would not come out of their society easily and thus additional travel by healthcare professionals would be required to reach those groups. This, in turn would result in increased intervention costs. Therefore, economic evaluations which consider these kinds of additional costs would be relevant for policy-makers in such settings.

"In practical terms, the important thing is the women from the poor families; they will not understand the language, apart from their own language" (I.14).

8.4.2.2.2 Data availability

Another issue mentioned by most of the informants was data availability and accessibility which can be a problem in many LMICs (I.1, I.3, I.9, I.10, I.14, I.16 & I.18).

"*This is very common in many countries when you ask any cessation clinic. They have it somewhere but it is not useable or not traceable"* (I.4).

"I do not think smoking is registered in medical records in many LMICs. In [redacted], for instance we as maternal care providers were not asking about this" (I.10).

Furthermore, fragmented healthcare systems were highlighted as another problem. In some countries, pregnant women are not followed by a specific family physician during their pregnancy and they admit to any health facility they would like to (I.12). Hence, follow-up and costing (I.6, I.9 & I.12) would be challenging in those settings.

8.4.2.2.3 Access to cessation services

The availability of publicly funded cessation services was acknowledged as another consideration. For example, the informants stated that in many countries in Asia and Africa where cessation services are available people pay for them out of pocket. In the Middle East on the other hand, it was reported that "ask & advice" was integrated into publicly funded primary care in most of the countries except for Somali and Sudan.

"*In my region, many countries do not have any kind of cessation service, anything available. I would say only 10-15% would be able to access these kinds of services."* (I.9).

This theme indicates that if countries do not have enough resources to put SDP interventions in place, the cost-effectiveness of an intervention would be irrelevant. For example, in some LMICs, they do not have sufficient funding to run special

cessation clinics whatever the cost-effectiveness of such an intervention (I.4). Additionally, economic evaluations from HICs should be adjusted to include the additional costs arising from the recruitment and training of healthcare professionals as well as additional intervention costs (e.g. travel). Furthermore, the uncertainties caused by insufficient data should be considered.

8.4.2.3 Potentially cost-effective interventions

The use of health economic evidence in LMICs would be highly dependent on the type of intervention being evaluated. Based on the interview findings, characteristics of potentially relevant interventions were identified.

8.4.2.3.1 Service provision

Most informants emphasised the importance of integrating cessation services for pregnant women into primary care and maternal care.

"If you say I will design a cessation intervention for pregnant women only in cessation clinics, I think we have very limited access, the same as any other cessation clinics because you do not ask everyone as part of the routine practice. So, you ask everyone, identify and advise and then refer to intensive care." (I.4).

Expectant mothers engage with healthcare services for pregnancy-related issues, hence this contact time would be an opportunity to address smoking cessation. This was also suggested as a solution to the challenge of finding funds for those interventions.

"…strategically this could be integrated into other projects. We have, for instance, funding for you know fighting TB, HIV or malaria in pregnancy. …Yeah, so I would not wait, if I am to provide guidance, for specific funding for tobacco, just integrate it into an existing package. Integrating it into training of HCPs, that will not cost much. And also have it as part of primary care interventions. It is feasible and it will not cost much, you know. Just adding some things to what they already do." (I.8).

Similarly, one informant talked about opportunistic cessation counselling based on their experience in [redacted] (I.10).

"….*women are generally waiting together to get antenatal care and during this time some health information is provided for them. This can be an opportunity*. *We could incorporate information on smoking or tobacco use to that*" (I.10).

8.4.2.3.2 Cocoon cessation

One of the most repeated views was having a household perspective and providing cessation counselling for all members of a family. One informant named this *"cocoon cessation*" (I.10) while another one used the metaphor of "*killing two birds with one stone"* (I.2). Informants who worked in Africa and Western Pacific mentioned some opportunities for including other family members and even extended family members.

There was consensus amongst all informants that partner involvement is not only important for helping the women but also potentially for reaching smoking men which are high in numbers in most LMICs. This was seen as an opportunity to get the support of policy-makers because designing an intervention including other family members

increases the target population, considering particularly the high prevalence of smoking among men in LMICs.

"I think women are quite good in country […] because they bring their husbands who smoke to the programme, you know, to help them quit. I see a lot of women, coming with their husbands because they feel that if the husband quits smoking it is good for them, you know, it is a good idea. Partners can support them. It is good not just for pregnant women but also men who are trying to quit smoking" (I.6).

8.4.2.3.3 Social support

Another suggestion was including social support as part of the interventions. This included involving community members as well. Interventions developed in harmony with the existing culture based on the characteristics of a society would be more likely to be effective (I.8). Also, peer support might reduce the cost of a SDP intervention since only a couple of people from each village would need to be reached by HCPs.

"In the Pacific we are very blessed to have women`s organisations that are very strong. So each country even every village tends to have, you know, a women's group. One opportunity you have there is that, another that kind of cultural aspect that elders you know giving advice to younger people. One potential we have is to build on that and kind of you know ask those people to be the champions or to be the message bearers.… So, they will have someone in their village that they know is there just to support them without any judgment" (I.2).

Similarly, involving the extended family members was suggested as a culturally appropriate way of supporting pregnant women in Africa.

"There is more in the African context because the, in the African context you have other, you have a bigger family. You know, it is the extended family. Because health for them is not an individual business. So the mother- and father-in-law, brothers and sisters, etc. because at some point they all have a role to play." (I.8)

8.4.2.3.4 Financial incentives

Since financial incentives were effective and cost-effective in HICs informants were asked to share their views about their potential in LMICs. Seven informants (I.6, I.10, I.11, I.12, I.13, I.15 & I.16) thought financial incentives might be effective in LMICs. In addition, two informants (I.14 & I.16) reported that in South Asia and South America there have been some financial incentive schemes for encouraging women to attend antenatal appointments and they have increased the attendance significantly.

"*Yes, yes, it would be more effective in LMICs and country […], much more than the UK and other high income countries actually. I think people who live in HICs can usually afford their needs but here it is much harder. So providing some incentives would be more effective here"(*I.11).

On the contrary, some informants did not believe they would be effective mainly because of the way they work (I.2).

"No, no, no. We just don't do this here. I just don't think it would work here. Because if you are a tobacco user and you are given vouchers to quit and if you are trying to get the vouchers… Unless it is ongoing like a salary it is not going to have long-term effects. I think it is important to make sure the motivation that make them quit is intrinsic not because of an external factor" (I.2).

Regarding funding, most of the informants stated that the necessary resources to provide financial incentives did not exist in LMICs. They were also worried about the long-term sustainability and ethical problems, for instance, non-smoking women pretending to be smokers to get the rewards by quitting.

"We don't have enough resources to provide financial incentives especially in the long-term although they work. It is quite challenging to find money for that. What we do is that we tell them if you actually quit you can save 2-3 dollars a day. So, that is the incentive for them. We don't even have money to start a cessation programme so finding money to provide vouchers is quite challenging" (I.6).

8.4.2.3.5 Long-term support

When asked about the high relapse rates in pregnant women especially after delivery, interviewees mostly focussed on the reasons for relapsing. "*You know, it is because, becoming normal, doing what you used to do before you got pregnant. Yeah, so, it is like a signal to say if I manage to start smoking, you know, that will be a signal that says now I am okay"(I.8).*

The majority of the informants felt that to reduce relapse rates long-term support should be provided.

"So, the idea that our healthcare providers who are there for the antenatal services are also there to encourage women to stop smoking and support them all the way through

because you have a great opportunity while they are pregnant women, that is quite a few months" (I.2).

"I would say one year after birth. Yes, because you know….In the African context, you know breastfeeding; it takes for the majority of the women at least one year. So, that I think is an opportunity and during this time they are still in touch with health system. So for me it is really an opportunity to continue supporting these women who are not spontaneous quitters" (I.8).

However, one informant stated that it would not be easy to reduce relapses in the long-term and referred to the high relapse rates among adults.

"*Whatever we do in general only around 30% of quitters remain abstinent in the long-term, like lifetime. This means 70% goes back to smoking; this is, because we don't have magic bullet"* (I.4).

8.4.2.4 Using economic evidence for policy-making in LMICs

The final theme was related to the use of economic evidence on SDP interventions in LMICs. Since one of the key objectives of IPHO was affecting health policies, it was important to understand which tools they used for decision-making. Hence, informants were asked what their decision-making process would be if they were to provide advice to a country on a smoking cessation intervention for pregnant women. All informants mentioned international guidelines, including WHO and EU guidelines. Additionally, they stated using scientific evidence (i.e. peer-reviewed journal articles) almost instantly. However, informants from LMICs talked about lacking scientific studies specific to their regions.

"*But in the region we do not have any evidence in this regard unfortunately"* (I. 7).

8.4.2.4.1 Country-specific evidence

Some informants emphasised the importance of context-related evidence and the specific features of that setting. This suggests that health economic evidence on the interventions that are feasible within country-specific conditions would be relevant. For example, cost-effectiveness of providing financial incentives for pregnant women would not be relevant in a country with no resources for such interventions. In addition, interventions would need to be relevant to local needs and opportunities (e.g. building on community organisations).

"*So, then you have to look at the local situation at first, you know. What are the trends? What are they doing? Prevalence of tobacco use in that specific setting"* (I.9).

"For example, community based interventions would be more feasible in low income countries while I would consider financial incentives in high income settings" (I. 8).

8.4.2.4.2 Policy-making

Using cost-effectiveness evidence to attract investments was a key point which was apparent when interviewees were asked whether they would use health economic evidence to influence health policy in LMICs.

"Yes, definitely, you know. I mean how can you convince a government? If you cannot prove that the effect relative to the cost would be higher. The cost-effectiveness issue is very relative. I mean, cost-effectiveness is definitely considered but the benchmark is set by countries not by our organisation" (I.3).

Interestingly, the senior cessation specialist at the headquarters (I.4) stated that they considered cost-effectiveness of cessation interventions while comparing cessation interventions with other interventions for non-communicable diseases, but when advising to a country on particular cessation interventions, they did not compare the cost-effectiveness of different cessation interventions. The IPHO had a predefined route, which included starting with the least costly service which would be accessible by the majority of the population and then adding other services (e.g. more intense interventions). Thus, affordability was the main consideration rather than cost-effectiveness.

Additionally, one informant (I.2) stated that public health and civil society organisations would use that evidence in their efforts to affect policy-making. However, the informants noted that politicians would not always rely on evidence to make decisions, stating although health economic evidence would be valued by some policy-makers in LMICs, there would need to be a general commitment to tobacco control to ensure the correct decisions are taken (I.10, 13 & 18).

"It depends of governments' commitment to tobacco control. Those highly committed, probably, would value and consider cost-effectiveness studies on smoking cessation. Others probably don't" (I.2).

8.5 DISCUSSION

This research aimed to explore the use of HIC-originated health economic evidence on SDP interventions for informing health policies in LMICs. With this aim an IPHO was chosen as a case study and semi-structured interviews were conducted with 18 informants who worked there. The key finding of this study is that health economic evidence on cessation interventions would need to take into consideration local characteristics to be viewed as relevant. For example, services that are integrated into primary care or maternal care services have the potential to influence health policies in LMICs. In addition, affordability is a key consideration. Hence, services which require less up-front investment would be considered as well as integration into existing services. Nevertheless, a number of factors might inhibit the influence of such evidence in some countries, including low anticipated prevalence of SDP, insufficient political will to take action against tobacco, and insufficient interest in cessation interventions. Therefore, there are applicability issues to be considered in addition to technical transferability.

The findings show that economic evaluations of SDP interventions would be more relevant in the LMICs where there is a high prevalence of SDP, such as Bulgaria. In the countries where SDP affects a small proportion of society, cost-effectiveness of SDP interventions may not be considered of importance because it would not be seen as a significant health problem by policy-makers. However, in some countries, there are some cultural or religious barriers that prevent the accurate identification of the number of women who smoke during pregnancy. Thus, the actual scale of SDP might

be greater than currently reported. Yet, policy-makers might be reluctant to focus on the issue due to the cultural norms and expectations around women's behaviour in pregnancy.

The findings about the prioritisation of SDP interventions indicate that an economic evaluation of cessation interventions may not be given attention in countries where strong tobacco policies are lacking. Even if a cessation intervention is highly cost-effective it would not be implemented widely if the country does not prioritise such interventions. Additionally, in countries where tobacco policies and general cessation services are in place, health economic evidence on SDP would be more relevant. Furthermore, in many countries tobacco control policies are preferred to cessation services. Thus nevertheless, cost-effectiveness evidence on cessation interventions for pregnant women may provide a starting point to attract investment in cessation interventions.

Furthermore, effectiveness of SDP interventions and the effects on health inequalities might differ. In most LMICs where tobacco use and smoking is more common among disadvantaged women, such interventions would have an impact on reducing health inequalities. However, in some other LMICs where tobacco use and SDP may be more common among the better off, it would not be the case. Thus, considering the difference in effectiveness and health equity impact would affect the use of health economic evidence in LMICs.

8.5.1 Cessation Intervention Models for Pregnant Women

This study identified the characteristics of potentially cost-effective cessation interventions for expectant mothers in LMICs. This included integration into maternal care and primary care, having a household perspective (cocoon cessation), social support, and long-term support. The mechanisms to provide those elements, however, would depend on the setting. For example, in countries where female smoking is culturally unacceptable, confidentiality would be a key consideration. Although some participants believed that financial incentives would be effective in LMICs, affordability and sustainability were the major concerns.

The study shows that one reason for the lack of prioritisation of SDP interventions is the low reported prevalence of SDP in most LMICs. Thus, health economic evidence on SDP interventions with a household approach to smoking rates would be useful, considering the high levels of male smoking in LMICs. Another reason for the reluctance of policy-makers in LMICs to support and invest in such interventions in the general population might be the high relapse rates. However, SDP interventions have positive impacts on infants and it is very important to protect children from smoke exposure during pregnancy, even if the mother relapses to smoking after pregnancy. Therefore, health economic evidence on SDP interventions with low relapse rates that also considers the long-term benefits of SDP interventions could have the potential to influence health policies in LMICs.

8.5.2 Strengths and Limitations

This study had some important strengths. Firstly, it was the first to explore the use of HIC-based economic evidence on SDP interventions in LMICs. This included identifying the characteristics of potentially cost-effective SDP interventions in LMICs. Secondly, the interviewed informants had experience in different parts of the world, enabling comprehensive coverage of a range of geographical area.

On the other hand, some limitations should be acknowledged. Firstly, the way of communication was not the same for all informants; some were interviewed face-to-face but some via video and phone calls, and in one interview an interpreter, a senior health economist, was present. However, the informants were comfortable with alternative forms of communication due to the nature of their jobs, and a rigorous process was followed with the interpreter to ensure the effect on the data was limited. Also, the author had different relationships with the informants; being only able to meet those who were working at the headquarters of the IPHO in person. This might have had an impact on their level of trust in relation to the researcher. Additionally, three of the interviews were not recorded (at the participants' requests), so the researcher relied on note-taking. However, the informants were happy to be contacted again if there was anything unclear. Therefore, the impact of this on the data should be limited.

Although an attempt was made to cover all of the IPHO regions, there might be some additional considerations for specific countries that were not covered by the informants in this study.

8.5.3 The Study in the Context of the Wider Literature

Few studies have considered the applicability of the health economic evidence generated in HICs to LMICs. The current study findings include some issues identified by Drummond et al. (2016). It is clear that economic evaluations which are easily adjustable to reflect countries' specific circumstances (e.g. increased transportation costs) would be able to provide more useful information for a range of settings. In the study by Drummond et al. (2016), the most repeated challenge for transferring health economic evidence to MICs was different practice patterns and the availability of facilities. The current study provides more specific details on that issue in the context of SDP interventions.

Moreover, the study identified some opportunities to overcome those challenges. For example, incorporating SDP advice into existing maternal care services and using existing social community structures (e.g. women's groups in the Pacific) to reach pregnant smokers were suggested, considering limited resources and facilities. Taking advantage of some cultural characteristics (e.g. extended family structure in Africa) to support pregnant women throughout pregnancy was another suggestion.

Some of the factors identified in this study are similar to those in the systematic review by Goeree et al. (2007) which looked at transferability of economic evaluations more generally. For example, different levels of education and socioeconomic status were cited as factors that would have an impact on effectiveness. In addition, the current study suggests that differences in the characteristics of SDP would influence the health inequality aspect of an intervention. Although Goeree et al. (2007) provided important guidance in transferring health economic evidence to different geographical areas there was no specific focus on LMICs. This analysis, however, identified elements which are specific to SDP in LMICs, such as the broader policy environment and the high level of smokeless tobacco use in some countries.

Additionally, some of the challenges identified in this study might be valid for many HICs too. For instance, a recent study conducted in the UK, investigating healthcare professionals' views on barriers and facilitators of smoking cessation during pregnancy and postpartum period reported *"lack of knowledge and confidence to advice about smoking in pregnancy"* as a problem (Naughton et al., 2018). Similarly, in terms of prioritising SDP, they highlighted that other healthcare initiatives or targets (e.g. reducing obesity) might cause SDP to be given less attention and this was stated during the interviews in this study too. This shows that competing healthcare targets affect prioritisation of SDP in LMICs and HICs.

8.5.4 Applicability of the PhD Findings in LMICs

This study shows that findings of this PhD thesis might be useful in LMICs in several ways. First, although the prevalence of smoking was raised as the main reason for SDP not being a priority in many LMICs, there are some countries with high prevalence of SDP, such as Turkey (15%) and Jordan (10%) (Caleyachetty et al., 2014, Lange et al., 2018). Thus, the PhD's modelling findings may be applicable to those settings. Additionally, although the PhD focuses on smoking cessation interventions, there is no known difference between smoking cessation and smokeless tobacco cessation techniques (Ebbert et al., 2015). Hence, the modelling findings could be useful for some LMICs where SDP rate alone is low, but tobacco use during pregnancy is high, including Madagascar (12%), Burundi (8%), and Cambodia (7%) (Caleyachetty et al., 2014). Furthermore, concerns over the accuracy of prevalence data indicate that the scale of the problem might be greater than anticipated in LMICs.

Secondly, features of a potentially cost-effective intervention identified by the interviews include incorporating long-term cessation support into maternal care because in almost all LMICs maternal care is provided even though funds for a standalone cessation intervention may not be available in many settings. In addition, reach would be wider if these services were provided by healthcare professionals who provide maternal care. The hypothetical interventions evaluated in Chapter 7 are midwife-centred, long-term interventions rather than standalone services. Therefore, those interventions could be used to create a model for LMICs too.

Similarly, having a household perspective is the key element of the hypothetical interventions in Chapter 7 and it is an important consideration in LMICs as well due to two main benefits. First is the increased support for women. The only SDP trial from LMICs included in the most recent review of psychological interventions found social support effective (RR= 1.83, 95% CI, 1.22-2.73) in helping pregnant South American women quit (Belizán et al., 1995). Additionally, given that SDP interventions offer a potential opportunity for reaching their partners and other family members, the analysis in Chapter 7 might be useful because smoking among men is very high in most LMICs (Sreeramareddy et al., 2018).

This research also indicates that there are some important limitations to the applicability of the PhD findings in LMICs. For example, women from lower socioeconomic groups are more likely to smoke during pregnancy than the better off in HICs (e.g. UK). However, in some MICs this may not the case based on the limited evidence on the issue. This would need to be taken into account as differences in the socioeconomic status of women who smoke whilst pregnant could have an impact on the effectiveness and costs associated with interventions. For example, financial incentives are found to be effective and cost-effective in the UK but they may not be as effective among women in some LMICs. In contrast, they may be more effective in some LMICs. Alternatively, the effectiveness of some interventions might be lower in some LMICs due to differences in educational backgrounds.

Investing in such interventions to address SDP is important in HICs to reduce health inequalities in societies. However, there is little evidence about the relationship

between socioeconomic status and SDP in LMICs. Thus, there is a need for further research on the socioeconomics of SDP to address the issue in LMICs. While evidence from HICs could have some relevance, care would be needed to ensure that social, economic and cultural differences are fully taken into account.

8.6 CONCLUSION

This analysis identified the challenges and opportunities in using health economic evidence to address SDP in LMICs. The study also showed that the PhD's modelling findings would be useful for health policy-making in many LMICs. However, some factors that may inhibit the applicability of the findings should be considered. Additionally, the characteristics of potentially cost-effective interventions in LMICs are similar to those in HICs according to the IPHO informants. Yet, those characteristics should be incorporated into the intervention design by considering the social, economic and cultural features of specific settings.

8.7 CHAPTER SUMMARY

This chapter presented a study exploring the applicability of HIC-based economic evidence on SDP interventions in LMICs. This included semi-structured interviews with 18 informants from an international public health organisation. The interviews were analysed using the framework method, which resulted with four key themes; policy context, implications of healthcare systems, potentially cost-effective interventions

and finally the use of economic evidence in LMICs. The succeeding chapter provides a summary of the whole thesis and the discussion.

CHAPTER 9: DISCUSSION

9.1 Brief Summary of the Thesis

The motivation behind this PhD work was the importance of tackling SDP as a key to reducing health inequalities and the limitations of current cessation services to reach pregnant smokers and provide comprehensive support. The PhD project aimed to improve the economic evidence available to inform decision-makers and design better SDP interventions by identifying the characteristics of optimum interventions. This included:

a-) systematically reviewing the evidence on health outcomes of SDP,

b-) developing an economic model to evaluate SDP interventions,

c-) evaluating hypothetical optimum interventions for pregnant women who smoke and

d-) exploring the applicability of high-income country based health economic evidence in low and middle-income countries.

Main findings of the thesis are summarised in this section.

9.1.1 Chapters 2 and 3: Background on SDP and Economic Evaluations

The theoretical background to the thesis was provided in Chapters 2 and 3. Chapter 2 summarised the significance of SDP in the UK and discussed the effectiveness of standard cessation support available to pregnant smokers. The chapter also presented the evidence on SDP interventions with a specific focus on financial incentives, which evidence suggests is the most cost-effective SDP intervention (Chamberlain et al., 2017). The chapter concluded that there was a lack of evidence regarding the impact of providing long-term support within a household approach alongside potential for higher amounts of financial incentives.

Chapter 3 introduced health economic evaluation methods, and discussed the limitations of existing economic evaluations of SDP interventions. A recent economic evaluation by Jones et al. (2018) overcame some of those limitations. However, the impact of partner smoking and the severity of smoking were not considered. Hence, it was decided to improve the ESIP model and produce a new economic model for assessing SDP interventions.

9.1.2 Chapter 4: Umbrella Review

To build an economic model it was necessary to identify the health outcomes to be included. Therefore, an umbrella review (systematic review of reviews) was conducted to determine the health outcomes of SDP and the postpartum period for the mother and offspring. The choice of an umbrella review rather than a standard systematic

review arose due to the considerable number of studies investigating the impact of SDP, as discussed in Section 4.1.2.

The review identified 63 systematic reviews reporting a wide range of conditions associated with SDP, such as infant death and intellectual impairment. Some of the conditions were found to have a causal relationship with SDP in the causal link analysis. A further step was considering the modelling-related practicalities. The study concluded that nine infant-related and five mother-related conditions having a causal link with SDP should be included in the economic evaluation. Additionally, the review found significant impacts related to partner smoking and the severity of smoking on mother-related and infant-related conditions.

9.1.3 Chapter 5: Developing an Economic Model for SDP Interventions

Chapter 5 outlined the development of a decision analytic model to evaluate SDP interventions. The chapter discussed the potential ways of improving ESIP and concluded that it could be improved by adopting a household approach through inclusion of partners and by including the severity of smoking. Another improvement was including SID, LRI and childhood obesity. This resulted in a new model being produced named ESIP.H.

ESIP.H is a dynamic cohort model with a household approach, using a lifetime horizon to capture the long-term impacts of SDP and parental SHS in childhood. Population risks were obtained from national datasets and the relative risks from the best

available evidence. Following the NICE guidelines, future costs and benefits were discounted at a rate of 3.5%. To deal with uncertainty, one-way sensitivity analyses and probabilistic sensitivity analysis were conducted.

The model produces standard health economic outcomes (e.g. incremental cost per quitter and cost per QALY) and return on investment (ROI) estimations. The differences between ESIP.H and ESIP are discussed in Section 5.3.

9.1.4 Chapter 6: Evaluating the MiQuit Intervention Using ESIP.H

Since ESIP.H was built by improving the ESIP model, a comparison of the two was conducted through an assessment of the MiQuit intervention which was a low-cost, text-based SDP intervention. Chapter 6 presented the results of this comparison, and the key findings are summarised as follows:

- According to both models, MiQuit was cost-effective when only the pregnancy period was considered and dominant in the lifetime analyses.
- ESIP.H estimated a lower ICER than ESIP for the pregnancy period, suggesting the intervention was more cost-effective than ESIP had reported.
- ESIP.H estimated greater cost-savings in the combined analysis for the mother and offspring and in the household analysis.
- Only in the mother lifetime analysis, ESIP.H found MiQuit to be less cost-effective than ESIP had calculated. The potential reasons for that are explained in Section 6.4.4.

Additionally, an Expected Value of Perfect Information (EVPI) analysis was conducted to estimate the value of reducing uncertainty around the model findings. The analysis found an EVPI of zero at a £30,000 per QALY threshold.

9.1.5 Chapter 7: Characteristics of Hypothetical Optimum SDP Interventions

Characteristics of optimum SDP interventions were explored in Chapter 7. Three hypothetical interventions were designed based on the available evidence and scenario analyses were conducted using the ESIP.H model. The first intervention (SFH3m) was designed based on the comprehensive report by Morgan et al. (2015), which consisted of NRT, behavioural support with midwife home visits, financial incentives and a household approach through inclusion of partner or significant other. The second (SFH12m) had the same characteristics with a longer-term support until one year after delivery. The third intervention (RSDP) was a reduction intervention designed for women who were not ready to quit, supporting them reduce smoking by delivery. RSDP also included NRT, professional behavioural support and financial incentives.

The analyses showed that SFH3m and SFH12m could help an additional 467 women and partners quit smoking at delivery in the base scenario and 286 women and partners in the cautious scenario, which resulted in significant improvements in health outcomes. For instance, in the hypothetical interventions, there were up to 10 fewer foetuses lost than in the control. According to the outputs of ESIP.H, both

interventions were dominant over the control in the lifetime in both scenarios. This study concluded that long-term and more intense financial incentive interventions that include partners or significant others in the household would provide considerable health benefits and they would be cost-effective.

Additionally, the RSDP intervention could help 730 women reduce smoking by delivery in the base scenario and 514 women in the cautious scenario. Moreover, RSDP produced an incremental 39 quitters amongst mothers one year after delivery in the base scenario and 27 in the cautious scenario. Like the cessation interventions, RSDP provided significant health benefits as well. For example, there were 12 fewer foetuses lost in the intervention compared to the control. RSDP was found to be cost-effective in the lifetime model in both scenarios. It was concluded that offering support to reduce smoking would improve health outcomes significantly and would be cost-effective. The reduction intervention is also important in widening the reach of cessation services for pregnant women.

9.1.6 Chapter 8: Informing Health Policy in LMICs

Since the data used in this thesis were HIC-based it was important to understand to what extent the findings would be useful to inform health policies in LMIC settings. The qualitative case study, including interviews with 18 informants working in an international public health organisation, addressed this issue. The interviews were analysed using the framework method (see Section 8.3).

The analysis identified four key themes; a) policy context, b) characteristics of healthcare systems, c) potentially cost-effective interventions and d) using economic evidence for policy making. It was found that SDP was not a priority in most LMICs and the main reasons for that were the low or underestimated prevalence of SDP, limited resources, competing health problems and a preference of tobacco control over cessation interventions.

The study identified the challenges and opportunities to use HIC-based health economic evidence to inform policy-making in LMICs. The study found that tobacco use during pregnancy was not a priority in LMICs, and economic evidence could be useful to prioritise SDP interventions. For instance, economic evidence on the SDP interventions with a household approach could be useful to increase the prioritisation of SDP interventions due to the high level of smoking in males. Economic evidence on the SDP interventions that take into consideration the country-specific features would be more relevant. For example, evidence on the SDP interventions integrated into existing services, or the interventions that involve community structures would be useful. Similarly, economic evaluations that could be adapted according to the setting specific features (e.g. training of healthcare professionals, additional travel costs) would be more relevant.

9.2 Strengths and Limitations of the Research

The strengths and limitations related to the specific chapters are discussed below.

9.2.1 Chapter 4: Umbrella Review

The health conditions to be included in the economic evaluations of SDP interventions were identified based on a systematic and comprehensive study. The previous evaluations of SDP interventions often did not follow a clear methodology for the inclusion of health conditions. Focussing only on systematic reviews resulted in including the health conditions for which a strong body of evidence have been produced. In addition to statistical associations, causal link and modelling practicalities were considered. Thus, the identification of health conditions to inform the modelling study was systematic and transparent.

To the best of the author's knowledge, this was the first umbrella review on the health impacts of SDP and the postpartum period. The review identified some health conditions that were not considered in the previous economic evaluations of SDP interventions. Additionally, the study supported the inclusion of the impact of the severity of smoking and partner smoking in the economic evaluation of SDP interventions.

There are some limitations to be acknowledged. Focussing only on systematic reviews published in English may have caused not including some significant health outcomes for which there yet to be enough evidence in English. However, the aim of the review was to inform an economic evaluation of SDP interventions in the UK, and hence this was justified.

9.2.2 Chapter 5: Developing an Economic Model for SDP Interventions

The economic model described in Chapter 5 is the only SDP model that adopts a household perspective and considers the severity of smoking. It overcame most of the limitations in the previous models and hence, it produces more accurate evidence than the existing models. Yet, due to lack of data and computational restrictions some assumptions were made. Limitations arising from model assumptions that could be summarised as follows:

Within pregnancy component (WPC):

- The impact of having a non-smoking partner is the same as not having a partner.
- Active smokers exposed to SHS have the same health risks as active smokers not exposed to SHS.
- The health risks amongst light smokers are always greater than those in former smokers exposed to SHS.
- SHS does not affect the risks of ectopic pregnancy and placenta previa.
- Former smoking does not have any impact on previa, abruption, pre-eclampsia, LBW and prematurity.
- Quitting early in pregnancy has the same impact as quitting towards the end of pregnancy.
- Unplanned pregnancy does not impact the probability of quitting.

Mother (MLC) and partner lifetime components (PLC):

- Living in a smoke-free house has the same impact as having a non-smoking partner.
- The model does not consider the impact of change in partner smoking status although it considers the impact of partner smoking status.
- Smokers do not change the number of cigarettes consumed after entering the model unless they quit smoking and relapse. Those who relapse can become light, moderate or heavy smokers.
- The probability of quitting amongst those who have never quitted before is the same as of those who quit previously and relapsed to smoking. Additionally, individuals can quit and relapse endless times.

Offspring childhood (OCC) and adulthood components (OAC):

- Although it is possible to enter different probability of SHS for the comparator and intervention groups, smoking parents do not change their smoking behaviour around the child after entering the model unless they quit.
- When both parents smoke, the probability of SHS exposure is identified by mother's severity of smoking.
- The severity of partner smoking does not have any impact on SHS probability and health outcomes.
- The impact of SHS on health outcomes is not included in the OAC.

- Mother's smoking just before or early in pregnancy does not increase the risk of SID or LRI although it increases the risk of asthma.
- After the age of 10, paternal SHS during pregnancy has no impact on the childhood asthma risk although SDP increases the risk by 23%.

The potential implications of those assumptions on the outputs of ESIP.H are discussed in Chapter 5 in detail. As a result of some assumptions, the model potentially underestimates the benefits of SDP interventions (e.g. former smoking does not affect LBW) while some other assumptions might cause overestimation (e.g. having a non-smoking partner is the same as not having a partner). Additionally, it is not possible to speculate on the impact of some assumptions (e.g. no transition between active smoking states) due to lacking data. Some of those limitations of ESIP.H could be overcome should new evidence become available (e.g. the impact of former smoking on preterm birth) while some are likely to be persistent due to the computational issues (e.g. limiting the number of quit attempts per individual). Hence, ESIP.H uses the best available evidence to provide accurate evaluations of SDP interventions, but the aforementioned limitations should be considered when interpreting its outputs.

In addition, ESIP.H uses HIC-based outcome data and English cost data and thus the outputs are limited regarding generalisability to other settings. Yet, it is a flexible model that could be reparameterised for any specific country.

9.2.3 Chapter 6: Evaluating the MiQuit Intervention using ESIP.H

The evaluation of MiQuit intervention in Chapter 6 demonstrated the value of ESIP.H and enabled a comparison with ESIP. The comparison showed that ESIP.H was able to produce accurate results, incorporating the impact of partner smoking and the severity of smoking.

In contrast to ESIP, a household analysis was conducted in ESIP.H, incorporating the partners in addition to mothers and offspring. That increased the expected lifetime cost savings from £64 to £213 (Section 6.4.3). Similarly, expected cost saving for per £1 invested rose from £21 in the mother and offspring analysis to £71 in the household analysis. Although the MiQuit intervention only targeted mothers, and it was assumed that it did not have any impact on partners' smoking at delivery, ESIP.H suggests that it generated significant health benefits to the partners by eliminating the impact of SHS by women in non-smoking partners, and increasing the probability of quitting in smoking partners after delivery. Thus, it is possible to estimate the spill-over effects with ESIP.H although a SDP intervention targets only women. The significance of considering the spill-over effects in economic evaluations has been discussed in the health economics literature (Al-Janabi et al., 2011, Brouwer et al., 1999, Fletcher and Marksteiner, 2017). Economic evaluations that do not consider the spill-over impacts on partners may underestimate the benefits of SDP interventions and cause suboptimal decisions. Therefore, the study makes an important contribution by estimating the impacts of a SDP intervention on partners for the first time.

Moreover, ESIP.H estimated two ROI analyses by assigning a monetary value to the QALY gains unlike ESIP that considered the healthcare savings only. Inclusion of QALY gains increased the expected ROI from £21 to £400 in the mother and offspring analysis and from £71 to £484 in the household analysis. Therefore, ESIP.H provides more comprehensive estimations that could affect decision-making.

Regarding the cost-effectiveness decisions for the mother and offspring, the two models produced similar findings although the expected health benefits and cost savings differed (see Section 6.4.5). This was because MiQuit was assumed to have no impact on partner smoking at delivery, the severity of smoking and postpartum relapse rates. Thus, it is expected that ESIP.H and ESIP would generate considerably different outputs when evaluating long-term SDP interventions especially if the intervention-specific impacts on the severity of smoking and SHS are also entered to the model.

Additionally, this analysis demonstrated the impact of adopting a lifetime perspective rather than focussing only on pregnancy since MiQuit was cost-effective in the within pregnancy analysis and dominant in the lifetime. In line with this, the ROI analyses showed that decision-making based on short-term outcomes would result with losing healthcare resources in the long-term (Section 6.4.3). Likewise, the findings indicated the importance of considering QALY gains as well as healthcare savings in ROI analyses.

It is important to note that this analysis was restricted by the limitations of data collected during MiQuit trial. For example, the proportion of women exposed to SHS was only measured at enrolment and hence there was no data on the impact of MiQuit on partner's quitting probability. Similarly, there was a lack of data regarding the

impact of MiQuit on postpartum relapse rates. Hence, ESIP.H might be underestimating the benefits of MiQuit if it provided any improvement in partner quit rates and postpartum abstinence amongst mothers. On the other hand, the estimations would be accurate if there was no such impact. Yet, this would not affect the comparison between ESIP and ESIP.H since the former did not include partners.

9.2.4 Chapter 7: Characteristics of Optimum SDP Interventions

Chapter 7 focussing on identifying the characteristics of hypothetical optimum SDP interventions made an important contribution to the literature in several ways. Firstly, it was the first economic evaluation of hypothetical optimum cessation interventions for pregnant smokers. Additionally, it was the first study to design and evaluate a hypothetical reduction intervention for women who were not ready to quit smoking.

The quit rate at delivery amongst mothers in the proposed interventions (44% in the base scenario) was considerably higher than those achieved in existing SDP interventions (Chamberlain et al. 2017). For instance, that figure was 23% in the CPIT study where women were provided up to £400 vouchers for quitting smoking (Tappin et al., 2015). Similarly, the proportion of four-week quitters in the NHS SSS was 29% (NHS, 2018). Thus, the hypothetical cessation interventions have potential to reduce the SDP rates and associated health problems. Additionally, 15% of smoking partners could quit with the hypothetical interventions (see Section 7.4.2). Therefore, the adverse impacts of SHS by partner during pregnancy could be averted as well.

There are also potential improvements regarding postpartum relapse rates. The bio-chemically verified relapse rate amongst women who quit at delivery was 80% in a previous trial (Ratner et al. 1999). In the CPIT study, 65% relapsed to smoking six months after quitting at delivery (Tappin et al. 2015). With the long-term cessation intervention lasting until one year postpartum, the relapse rate could decline to 34% while it could be 45% with the cessation intervention lasting until three months postpartum (see Section 7.4.2). Hence, the hypothetical interventions have the potential to reduce the adverse health impacts of postpartum smoking considerably.

Furthermore, currently less than a quarter of expectant mothers engage with the NHS SSS (NHS, 2018). The reduction intervention conceptualised in this study offers a way of reaching more women by supporting expectant mothers who are not ready to quit. The reduction intervention could reduce the proportion of heavy and moderate smokers significantly as well as producing 38 additional quitters one year after delivery (see Section 7.4.2). This indicates that it is possible to increase the number of quitters in the year after delivery as well as reducing the adverse pregnancy outcomes.

The economic evaluation showed that despite being more costly than the control, all the hypothetical interventions were cost-effective in the lifetime analyses. Moreover, the cessation interventions were dominant when the impacts on partners were also considered in both scenarios. Previously, the economic evaluation by Boyd et al. (2016) estimated that offering up to £1,800 per woman would be cost-effective. The current economic evaluation with ESIP.H found that offering incentives up to £2,320 per household would be cost-effective. Thus, the study supports allocating more resources

to such SDP interventions. It is hoped that the findings would be useful for decision-makers in designing SDP interventions with a greater impact than the current NHS SSS.

This study was conducted based on hypothetical scenario analyses. This required making some assumptions about the effectiveness and costs based on the best available evidence. However, the number of studies was limited and they were conducted in Scotland and the USA. Thus, the actual figures on the effectiveness and costs might be different than estimated in this study. To deal with that, a conservative approach was taken in the estimations, with the cautious scenario illustrating pessimistic assumptions for comparison with those used in the base scenario. Despite the differences in the ICER estimates, the decisions regarding cost-effectiveness outcomes did not differ in the two scenarios. Thus, the conclusions would not change significantly if the analyses were conducted based on the cautious scenario only. Furthermore, the cautious scenario demonstrated the impact of the assumptions made for the base-case analysis. Thus, presenting two scenarios was useful for the purpose of the thesis, since there was no published evidence on the impact of long-term interventions combining a household approach with financial incentives.

The generalisability of health economics findings to other settings is limited since ESIP.H used England-based data. Yet, the characteristics of optimum cessation interventions might be relevant to many other countries. Thus, it would be interesting to conduct evaluations for different settings after reparameterising the model.

Another consideration is that the hypothetical interventions in this study included individual intense counselling delivered by trained midwives that lasted one hour.

However, there are some other behavioural support methods such as group therapy and motivational interviewing, and the comparative effectiveness of such interventions along with financial incentives could be addressed should new evidence become available.

9.2.5 Chapter 8: Informing Health Policy in LMICs

Chapter 8 reported the first study investigating the applicability of HIC-based economic evaluations of SDP interventions in LMICs. The study shows that the evidence produced in this PhD has the potential to inform policy-making in LMICs.

There is limited evidence on the impact of socioeconomic status on SDP or smoking amongst women in LMICs (see Section 8.1.1). In contrast to HICs where SDP is a health inequality issue, some studies suggest that it may not be the case in some MICs because women with higher income and higher education tend to smoke more, such as Albania and Turkey (Aslan et al., 2014, Hosseinpoor et al., 2012). However, according to the current study, the cultural norms that see female smoking unacceptable should be taken into account. As a result of that social phenomenon, women with higher education would be more comfortable to disclose that they are smoking. Therefore, the evidence on health inequality aspect of SDP in MICs is not conclusive.

The potential to inform health policy in LMICs is dependent on country specific conditions. Some findings would be applicable to all LMICs while others would be

relevant under certain conditions. For example, interventions delivered in antenatal-care settings would be socially acceptable, feasible and potentially cost-effective in all LMICs. Similarly, incorporating other smokers at home would be appropriate because of the high level of smoking amongst males.

However, if there are no resources for providing financial incentives, that characteristic of the interventions proposed in this study would be irrelevant for those settings without external funding. In addition, more evidence is required to understand the effectiveness and cost-effectiveness of financial incentives in LMICs since there were mixed views on that.

Additionally, the study provides guidance on the applicability of economic models of SDP interventions in LMICs, and the ESIP.H model might potentially be useful in LMICs since it considers partner smoking and SHS by parents. While the model parameters could be updated to those of any specific country, the study findings related to limited data availability in LMICs suggest that this would pose a significant challenge.

9.3 Use of ESIP.H

It is anticipated that ESIP.H would be a useful tool for national policy-makers (e.g. NICE) to evaluate SDP interventions and for local decision-makers to design their smoking cessation services for pregnant women. As discussed, the model presents an improvement on existing models and produces results in terms of both return on investment as well as cost-effectiveness.

The ESIP model developed by Jones et al. (2018) overcame many limitations of the previous economic models (Section 3.8.1). ESIP is useful if the decision-maker is interested in the benefits of short-term SDP interventions on only mother and offspring. Building on this model, ESIP.H is capable of estimating the impacts on partners, the severity of smoking and postpartum relapse rates. ESIP.H can also evaluate reduction interventions that are aiming to support pregnant women who are not ready to quit. Furthermore, ESIP considers only healthcare cost savings to calculate the ROI while ESIP.H produces two different ROI estimates based on healthcare cost savings only and QALY gains as well as healthcare cost savings. As a result, ESIP.H produces more comprehensive outputs based on more recent evidence (Section 5.3).

The Tobacco ROI tool developed by NICE has significant limitations in evaluating SDP interventions. Firstly, it does not consider the impact of partner smoking or the severity of smoking. Additionally, it neither includes the cost of pregnancy-related health conditions (e.g. ectopic pregnancy) nor the long-term offspring-related health conditions (e.g. asthma, smoking uptake) because of capturing only the first five years of offspring. Therefore, ESIP.H provides a more accurate estimation than the NICE Tobacco ROI tool.

Additionally, it is possible to use ESIP.H outside England after reparameterising the model to incorporate country-specific data. Furthermore, the use of ESIP.H is not limited to SDP; it can be used to assess interventions that aim to reduce SHS or generate smoke-free homes. Similarly, the model could be used to evaluate alcohol or

other substance use during pregnancy after reparameterisation and small structural changes.

An online version of the model will be made available on the UK Centre for Tobacco and Alcohol Studies website (http://www.ukctas.ac.uk/) where the previous version of the ESIP model is also accessible. This will enable policy-makers, decision-makers and researchers to benefit from the model.

9.4 Policy Implications: Addressing Health Inequalities

There has been a decline in the population of smokers and in the proportion of pregnant women who smoke during the last three decades in high-income countries, including the UK. However, smoking does not occur at the same rate throughout society, and it is a key driver of health inequalities in the UK (Jha et al., 2006). Therefore, investing in smoking cessation programmes has been identified as one of the major focus areas to reduce inequalities in health (Marmot and Bell, 2012, McLeod, 2018). Given that SDP is more prevalent among women from low socioeconomic backgrounds, SDP interventions have a great potential to reduce health inequalities.

SDP has been listed amongst the 12 indicators of national health inequalities, and the UK government has set a target of 6% or less for SDP by the end of 2022 (Department of Health, 2017). However, the current SDP rate (11%) indicates that it is very unlikely to achieve the target on time (HSCI, 2019). As discussed in Section 2.3.2, NHS SSS for

pregnant women fail to reach the majority of pregnant smokers and the service has very limited impact amongst those who engage with it (NHS, 2019b). Moreover, the spending for SSS recently declined around 30% by local authorities due to national austerity policies (ASH, 2019). Thus, there is an important gap between the stated policy aims and funding priorities.

The findings of this thesis suggests that cessation interventions that entail a more intense and long-term, midwife-based support together with a household approach are likely to be the most cost-effective. This would help reducing the gradient in health through increased number of quitters, reducing relapse rates after pregnancy, and reducing SHS exposure during and after pregnancy. Additionally, such SDP interventions reduce the number of individuals who start smoking since children of smoking parents are more likely to smoke (Leonardi-Bee et al., 2011). The reach would also increase as a result of providing the cessation support via home visits by midwives who support women during and after pregnancy rather than stop smoking specialists in cessation clinics.

The other approach suggested by the findings of this research is to focus on the reduction of cigarette consumption. Offering support to those who are not yet ready to quit entirely would also widen the reach of SSS for pregnant women as well as providing significant health benefits. Furthermore, since the probability of quitting is greater amongst women who are light or moderate smokers than in heavy smokers, the reduction intervention could increase the number of quitters in the long-term.

Given the budget constraints, a major concern for decision-makers would be the increased costs of providing such interventions. This study has shown that investing in more comprehensive and more costly SDP interventions is cost-effective. Hence, allocating more resources to such interventions would close the gap between policy and practice, increasing the probability of achieving the 6% SDP target. Moreover, recently, the Long-term Plan generated by NHS England has promised funding for specific, evidence-based interventions that tackle health inequalities, including SDP interventions (NHS England, 2019). This funding could be an appropriate resource for such interventions in local authorities.

9.5 Public Acceptability of Financial Incentives in the UK

Public acceptability of financial incentives is an important consideration since taxpayers money would be used to fund financial incentives interventions to reduce SDP. The Citizens Council organised by NICE concluded that providing financial incentives for smoking cessation in the general population was acceptable but concerns were raised over lack of robust evidence on the effectiveness of incentives (NICE, 2011b). Likewise, according to a recent discrete choice experiment, providing financial incentives for adult smokers was considered acceptable by the public in the UK (Giles et al., 2016).

When it comes to providing incentives for pregnant women, however, public opinion differs. In a comprehensive survey conducted by Morgan et al. (2014) the acceptability of financial incentives was assessed from the perspective of general public (n=1,144)

and health professionals (n=519). Around 42% of public members disagreed with the idea of providing financial incentives for women who quit smoking during pregnancy while 41% was in favour. The net disagreement rate was 46% for women who remained abstinent after delivery, and 37% supported it.

Responses from the health professionals were very similar to those of the public, with % disagreement. When asked whether local health services should be provided with extra funding for targets achieved in relation to the number of women who quit smoking, the majority (53%) agreed. Hence, most of the health professionals who participated in this survey stated that pregnant women should not be incentivised for quitting but that local health professionals should be incentivised for helping pregnant women to quit, which warrants further research on the reasons behind this.

Morgan et al. (2015) acknowledged the possible impact of economic constraints following the 2008 economic crisis and NHS reforms on their findings. A more important consideration is that, the participants were not provided with the information that financial incentives were the most effective and cost-effective SDP interventions. Therefore, the existing evidence on public acceptability of financial incentives is not sufficient to reach a conclusion on whether the taxpayers in the UK would support novel SDP interventions with long-term health impacts.

However, the wider evidence shows that public acceptability of financial incentives is significantly affected by the evidence on the effectiveness. Promberger et al. (Promberger et al., 2012) found that increasing the effectiveness of a smoking cessation intervention from 10% to 40% resulted with the agreement levels to rise

from 45% to 70%. Thus, it could be argued that the SDP interventions proposed in this thesis might be found acceptable by a larger proportion than Morgan et al. (2014) found, considering the high level of estimated effectiveness.

9.6 Future Research

The thesis outlines some potential future work. Firstly, a feasibility study to explore the patient and provider perspectives on the suggested trials would be needed. Conducting a pilot study to test the suggested intervention models in Chapter 7 would be the next step in designing SDP interventions with sustained impact. This is because the exploratory study in Chapter 7 shows that long-term, intensive financial incentives interventions with a household approach are promising. This pilot study would also enable to demonstrate the use of ESIP.H based on intervention-specific data.

There are some considerations for the piloting of the hypothetical interventions. The potential retention imbalance due to the use of financial incentives in the interventions should be considered since this may lead to bias in the findings. Another consideration is that currently, there is not any standard on the biochemical verification of reduction in smoking during pregnancy, which would pose a difficulty in using contingent financial incentives suggested in this study. Hence, some research is needed to develop methods for verifying reduction amongst pregnant women.

Related to the public acceptability of financial incentives, further research is required to gain more insight on the issue in the light of recent evidence showing that financial

incentives are the most effective and cost-effective SDP intervention in the UK (Chamberlain et al., 2017).

Additionally, there is some methodological work that warrants attention. For example, reparameterising the model for women from low socioeconomic groups and comparing the outputs with the current version would be interesting. Similarly, the inclusion of e-cigarettes to the economic model would be a valuable contribution. The practicalities around those are discussed in Section 5.3.

Another potential area would be using ESIP.H to evaluate a SDP intervention in LMICs. As discussed in Section 5.3, this would require identifying context-specific parameters which may not be readily available for every component of the model. In addition, the limitations around using HIC-based evidence in LMICs identified in Chapter 8 should be considered.

Furthermore, it would be possible to conduct economic evaluation of SHS prevention interventions with ESIP.H. There are some smoke-free home interventions aiming to reduce the SHS exposure amongst children and teenagers (Passey et al., 2016). Those interventions could prevent smoking uptake in adolescents as well as eliminating many health problems. They are also important in widening the reach of smoking cessation services since they offer help for parents who are not ready to quit. The only economic evaluation of smoke-free homes interventions was a cost-effectiveness analysis focussing on air quality and quit rates (Renwick et al., 2018). It would be interesting to estimate the impact of such interventions on lifetime health and cost outcomes, using ESIP.H.

In addition to those, the thesis identified some areas where further evidence was needed as follows:

- The probability of quitting one year after delivery amongst mothers who smoked throughout pregnancy
- Long-term postpartum relapse rates amongst partners who quit during pregnancy
- Long-term postpartum relapse rates (until two years postpartum) among women and partners who quit smoking before or early in pregnancy
- Impact of partner's smoking on women's smoking behaviour during and after pregnancy
- Protective impacts of SDP on pre-eclampsia, hyperemesis gravidarum and skin defects
- Dose-dependent impact of SDP on adverse health outcomes
- The combined impact of SDP and SHS during pregnancy
- The impact of former smoking on previa, abruption, pre-eclampsia, LBW and preterm birth

CHAPTER 10: CONCLUSION

Tackling smoking during pregnancy is a key to reducing health inequalities in society due to the increased morbidity and mortality risks for those predominantly in lower socioeconomic groups. Yet, the current support for expectant mothers who smoke is limited because most women do not engage with the NHS SSS, and the quit rate at delivery amongst those who enrol is low. Moreover, the majority of those who quit smoking relapse within a year of delivery. Thus, reducing SDP and postpartum smoking requires re-designing the smoking cessation support for pregnant women.

This PhD work makes a valuable contribution to the literature in several ways. Firstly, it presents a novel economic model (ESIP.H) that can evaluate SDP interventions more accurately than the previous models. ESIP.H is the first economic model adopting a household approach as well as considering the severity of smoking. In contrast to the existing models, ESIP.H is capable of assessing the impact of SDP interventions on partners, postpartum relapse rates, and the second-hand smoke exposure of the offspring. The development of the model was informed by a systematic and comprehensive review of the health outcomes of SDP. ESIP.H can be used to design better services for pregnant women.

This PhD project conceptualised two hypothetical cessation interventions with a household approach and one hypothetical reduction intervention. All the interventions were found to be cost-effective.

The hypothetical cessation interventions could generate up to 10 times the quitters amongst mothers that typical interventions have achieved. The cessation interventions could make a substantial impact on achieving the national ambition of 6% smoking rate amongst mothers at the time of delivery. That requires generating 25,000 quitters amongst 64,000 expectant mothers who smoke which is unrealistic with the current standard support for pregnant smokers, considering the services generate approximately 4,000 quitters at four-weeks in 14,000 who are enrolled to the NHS SSS. The hypothetical interventions have the potential to reach a higher number of pregnant smokers because they are to be delivered by midwives who are in touch with the women throughout the pregnancy unlike the NHS SSS which relies on a referral system. Additionally, offering financial incentives might also attract more pregnant women to be involved. The modelling found that the hypothetical interventions would have a considerable impact on the number of quitters, offering the potential to dramatically reduce SDP.

Moreover, the findings show that the hypothetical interventions could increase the number of women and partners who quit smoking during pregnancy and stay abstinent for a long period which would also reduce SHS and smoking uptake in children. Therefore, the hypothetical interventions could contribute to reducing smoking not only amongst pregnant smokers but also in the general population.

The characteristics of the optimum cessation interventions have significant implications. First, adopting a household approach through inclusion of partners could also produce significant health benefits for partners by increasing the quit rate from

3% to 15%. Helping smoking partners quit also results with 290 smoke-free households per 1,000 participating pregnant smokers. Furthermore, having a household approach changes the lifetime incremental cost from +£855 to -£675 and makes the interventions 'dominant'. This provides stronger evidence that might make the findings more attractive to decision-makers under the budget constraints.

Second, more intense behavioural support by a midwife, and offering high level of financial incentives, that is up to £1,520 per household contingent on abstinence, is a key characteristic. This is estimated to generate 350 additional quitters amongst mothers and 116 extra quitters in smoking partners, per 1,000 participating pregnant smokers. Providing the incentives along with the behavioural support until three months postpartum may reduce the otherwise 80% relapse rates to 64% in mothers and 76% in partners. Continuing the intervention until 12 months after delivery with up to a total incentive of £2,320 per household is estimated to generate 56% relapse rates amongst mothers and 62% in partners.

The hypothetical reduction intervention aims to support women who are not ready to quit reducing smoking by the time of delivery, and so widens the reach of cessation services as well as improving the health outcomes. The main benefit of this intervention is the reduced health risk through a reduction in the number of cigarettes consumed daily. Additionally, those who smoke fewer cigarettes are more likely to quit smoking later in life and also less likely to expose their children to SHS. Women are offered behavioural support and up to up to £640 contingent on a 50% or more reduction in smoking. The intervention is estimated to support 730 moderate or heavy

smokers to become light or moderate smokers, respectively, per 1000 participants. As well as producing significant improvements in the pregnancy outcomes, the intervention could generate 38 additional quitters amongst mothers one year after delivery.

Two different scenario analyses, the base-case and the cautious-case, were designed in response to the limited evidence. This method enabled estimating the potential impacts of the assumptions about the effectiveness and costs of the hypothetical interventions. The consistent findings of the cautious-case and base-case analyses provide a robust evidence base for the potential of the hypothetical interventions proposed in this thesis. The evidence produced through the modelling studies suggests that there is a strong case for allocating resources to longer-term and comparatively costly SDP interventions. Thus, much greater impact on addressing health inequalities could be achieved but only if decision-makers are willing to take a long-term view to generating health benefits, rather than seeking short-term cost savings.

Another contribution of the PhD work is that it provides a framework for using HIC-based economic evaluations of SDP interventions in LMICs. The case study of an international public health organisation found that integrating the cessation support to antenatal care and adopting a household approach are relevant to all LMICs. However, affordability is a key consideration in LMICs, and as a result, a focus on antenatal care would be appropriate. The ESIP.H model could be used to explore alternatives, using estimates for local costs and outcomes.

In conclusion, piloting the SDP interventions conceptualised and evaluated in this thesis offers value for policy-makers in the UK and potentially in some LMICs. Although it is not possible to eliminate inequalities in society, we can reduce its impact on health inequalities by supporting the most vulnerable. This thesis is hoped to contribute to that cause.

APPENDICES

Appendix 1. Medline Search strategy

1. pregnan*.mp.
2. exp Pregnancy/
3. postpartum.mp. or exp Postpartum Period/
4. 1 or 2 or 3
5. exp Smoking/ or smok*.mp.
6. exp Tobacco/ or tobacco.mp.
7. 5 or 6
8. 4 and 7
9. pregnancy outcomes.mp. or exp Pregnancy Outcome/
10. birth outcomes.mp. or exp Infant, Newborn/
11. exp Child Development/ or childhood outcomes.mp.
12. exp Risk Factors/ or adverse outcomes.mp.
13. "quality of life".mp. or exp "Quality of Life"/
14. "long-term outcomes".mp. or exp Follow-Up Studies/
15. 9 or 1 0 or 11 or 12 or 13 or 14
16. 8 and 15
17. systematic review.mp. or exp "systematic review"/
18. meta-analysis.mp. or exp Meta-Analysis/
19. 18 or 19
20. 16 and 19
21 . limit 20 to (English language and humans)

Appendix 2. Data extraction tool

Date
First Author & Publication Year
Study Focus
Mother or Infant Investigated (M/I)
Meta-analysis (Y/N)
Years Included
Databases Searched
Any Limitations to Database Search
Setting/Country of Included Studies
Number of Included Studies
Main Outcomes
Heterogeneity
Quality Assessment Tool
Dose-response Test
Partner Inclusion
Number of Exposed
Number of Unexposed
Number of Affected
Number of Not Affected
First Author & Publication Year
Study Focus
Years Included
Databases Searched
Any Limitations to Database Search
Setting/Country of Included Studies
Number of Included Studies
Main Outcomes
Heterogeneity
Quality Assessment Tool
Dose-response Test
Partner Included

Appendix 3. Quality assessment tool

No	*Statement*	*YES/NO/ NA/ UNCLEAR*
1	Was a protocol prepared prior to the review?	
2	Was the review question clearly defined in terms of population, interventions (phenomena of interest), comparators, outcomes and study designs (PICOS)?	
3	Was the search strategy adequate and appropriate?	
4	Were there any restrictions on language, publication status or publication dates?	
5	Were preventative steps taken to minimise bias and errors in the study selection process?	
6	Was quality assessment done?	
7	Were preventative steps taken to minimise bias and errors in the quality assessment process?	
8	Were preventative steps taken to minimise bias and errors in the data extraction process?	
9	Were adequate details presented for each of the primary studies?	
10	Were appropriate methods used for data synthesis?	
11	Were differences between studies assessed?	
12	If studies were pooled, and so was it appropriate and meaningful to do so?	
13	Was heterogeneity tested?	
14	Were the causes of heterogeneity assessed?	
15	Was publication bias assessed?	
16	Do the authors' conclusions accurately reflect the evidence that was reviewed?	

Appendix 4. Characteristics of included reviews

First Author & Year	Meta-analysis	Focus	M/I	Years Included	Databases Searched	Any Limitation	Setting	Quality Score
Ananth 1999	Yes	Placental abruption & SDP	M	1966 to 1997	MEDLINE	English only	Mostly HICs	**8**
Ankum 1996	Yes	Risk factors for ectopic pregnancy	M	1978 to 1994	MEDLINE	Studies in English, French, German, Dutch	Not provided	**7**
Antonopoulos 2011	Yes	Lympoma & SDP	I	All by Aug. 2010	Medline, Embase, Scopus, Google Scholar, Ovid and the Cochrane Library	Not Specified	HICs	**12**
Brion 2008	Yes	Blood pressure & SDP	I	Not provided	Not provided	Studies were included if the sample size > 100	Not provided	**7**
Burke 2012	Yes	Asthma and wheezing & SDP and passive smoking	I	1997 to Feb. 2011	Medline, Embase, Cumulative Index to Nursing and Allied Health Literature, AMED, and conference abstracts	Restricted to children (0-18), prospective cohort studies only, only English studies, studies ascertained smoking status at the same time as disease outcome not included	Mostly HICs	**13**
Castles 1999	Yes	Pregnancy complications & SDP	M	1966 to May 1995	MEDLINE and Current Contents	English studies only	HICs	**7**
Chao 2014	No	Risks for tourette syndrome	I	All by October 2012	Medline, Embase and PsycINFO	English and French studies	Not provided	**7**
Chrestani 2013	No	Risks for accelerated growth in childhood	I	Not stated	PubMed/ MEDLINE	Children aged between 0 and 12 years, studies in English, Portuguese or Spanish, studies including "catch-up" as an outcome	HICs	**8**

Chu 2016	Yes	Childhood neuroblastoma & SDP	I	1946 to Jul. 2014	PubMed, EMBASE, Cochrane Library, and ISI Web of Science	English studies only	HICs	**12**
Clifford 2012	No	Cognitive parameters of children and young adults & SDP	I	Jan. 2000 to Dec. 2011	Medline, Science Direct, Google Scholar, CINAHL, EMBASE, Zetoc and Clinicaltrials.gov	Passive smoking by pregnant women who were non-smokers was not included	HICs	**6**
Conde-Agudelo 1999	Yes	Pre-eclampsia & SDP	M	1966 to 1998	MEDLINE, Embase, Popline, CINAHL, Lilacs	The definition of pre-eclampsia corresponded to hypertension after 20 weeks' gestation plus proteinuria	Mostly HICs	**13**
England 2007	No	Pre-eclampsia & SDP	M	All by Mar. 2006	MEDLINE	English only	HICs	**7**
Faiz 2003	Yes	Placenta previa & SDP	M	Jan. 1966 to Mar.2000	MEDLINE	English only	Mostly HICs	**12**
Fernandes 2015	No	Vision difficulties & SDP	I	1985 to 2013	MEDLINE, EMBASE, Global Health, PsycINFO, Scopus, Web of Science and Google Scholar	Studies assessing children aged 0–18 years, Studies with comparable groups	Mostly HICs	**10**
Ferrante 2014	No	Asthma & smoke exposure	I	Jan. 2010 to Dec. 2013	PubMed and Scopus	Not Specified	Not provided	**6**
Flenady 2011	Yes	Risks for stillbirth	I	1998 to 2009	Medline (PubMed and Ovid), CINAHL, and the Cochrane Database of Systematic Reviews	English studies only, stillbirth definition of "20 weeks' gestation or more or a birthweight of min. 400gr."	HICs	**11**

Hackshaw 2011	Yes	Birth defects & SDP	I	1959 to 2010	MEDLINE	Only English studies	Mostly HICs	**12**
Huang 2007	No	Oveweight or obesity & prenatal factors	I	Jan. 1975-Dec.2005	PubMed and MDConsult	Only English studies including children aged between 5 and 21	Not provided	**5**
Huang 2014	Yes	Brain tumors & SDP	I	All by Jan.2014	PubMed and Embase	Not Specified	Mostly HICs	**14**
Huang 2016	Yes	Risks for non-genetic intellectual disability	I	All by Sept. 2015	Medline and Embase	Studies providing min. information to estimate RRs were included.	HICs	**11**
Huncharek 2002	Yes	Brain tumors & SDP	I	Jan. 1966 to 2001	MEDLARS, EMBASE, CancerLit	Pediatric patients only	Not provided	**11**
Ino 2010	Yes	Obesity & SDP	I	Jan. 2000 to Ap. 2008	PubMEd	English only	HICs	**9**
Jayes 2016	Yes	Respiratory health & smoking	M & I	All by 2013	MEDLINE, Embase, and Web of Science	Not Specified	Mostly HICs	**13**
Jenabi 2017	Yes	Hypremasis gravidarum & SDP	M	All by Jan. 2016	PubMed, Web of Science, and Scopus	No limitation	Mostly HICs	**10**
Jones 2011	Yes	Lower respiratory infections & household smoking	I	1997 to Nov. 2010	MEDLINE and EMBASE	Comparative epidemiological studies, no language restriction during the search but reported English studies only	Mostly HICs	**14**
Jones 2012	Yes	Middle ear disease & parental smoking	I	Jan. 1997 to Dec. 2010	MEDLINE, EMBASE, and CAB abstracts	Only English studies were reported	Mostly HICs	**13**

Kantor 2016	Yes	Atopic Dermatitis and smoke exposure	I	1823 to 2015	MEDLINE, EMBASE, Scopus, and Cochrane Library	Not Specified	Not provided	**12**
Lancaster 2010	No	Risk factors for depressive symptoms	M	Jan. 1980 to Mar. 2008	PubMed, CINAHL, SCOPUS, PsycINFO, Sociological Abstracts, ISI Proceedings, ProQuest Dissertations &Theses.	English only, studies with more than 20 subjects were included	HICs	**9**
Latimer 2012	No	Risks for disruptive behaviour disorders	I	Jan. 1966 and 31 Ap. 2009	PsycLIT/PsycInfo, BNI, CINAHL, EBM, EMBASE, ERIC, MEDLINE, Social Science Citation Index, and Science Citation Index.	Studies including assessment of factors present antenatally and in the first four years of life	Not provided	**7**
Lee 2013	Yes	Congenital heart defects & SDP	I	1947 to July 2011	Medline (Ovid and PubMed)	English studies only	Mostly HICs	**10**
Linnet 2003	No	Maternal risk factors for attention deficit hyperactivity disorder	I	1966 to January 2002	PubMed, MEDLINE, EMBASE, and PsycINFO	Children aged four years and older	HICs	**6**
Little 2004	Yes	Oral clefts & SDP	I	1966 to 2002	EMBASE and MEDLINE	Not Specified	Not provided	**9**

Marufu 2015	Yes	Stillbirth & SDP	I	All by 31 December 2012	MEDLINE, EMBASE, Psych Info and Web of Science	Stillbirth was defined as "fetal loss or death at 20 weeks gestation and above"	Mostly HICs	**14**
Mitchell 2006	Yes	SID& SDP	I	Not provided	MEDLINE and EMBASE	Not Specified	Mostly HICs	**6**
Nicoletti 2014	Yes	Birth defects & SDP	I	1950 to Ap. 2010	MEDLINE, LILACS and SciELO	Not Specified	Mostly HICs	**14**
Oken 2008	Yes	Overweight & SDP	I	1966 to Jun. 2006	Medline	Children older than two were included, studies used only a continuous measure of adiposity were not included in the meta-analysis, no language limit was defined but selected studies were all in English	HICs	**10**
Park 2008	Yes	Intrauterine tobacco exposure & breast cancer risk in the females	I	Jan. 1966 to Feb.2007	MEDLINE	English only	HICs	**9**
Pereira 2017	Yes	LBW & SDP	I	1984 to 2016	Medline, Embase, LILACS, SciELO, Web of Science, and Scopus	Not Specified	Mostly UMICs	**13**
Pineles 2014	Yes	Miscarriage & SDP	M	1956 to Aug. 2011	PubMed	Only studies comparing women who were exposed and those who were not exposed to tobacco smoke from cigarettes included	Mostly HICs	**11**

Pineles 2016	Yes	Perinatal death (stillbirth and neonatal death) & SDP	I	1956 and Aug. 31, 2011	PubMed	Not Specified	Mostly HICs	**12**
Rayfield 2017		Childhood overweight and obesity & SDP	I	All by Jan. 2015	PubMed, EMBASE, Global Health and Cinahl and Web of Science	Children born at full term (>37 weeks), overweight measured between 2 and 18 years	Mostly HICs	**14**
Riedel 2014	Yes	Childhood obesity & SDP	I	1900 to 2013	MEDLINE, EMBASE and Web of Knowledge	English only	Mostly HICs	**11**
Rosen 2014	Yes	Autism & SDP	I	All by Dec. 2013	Pub Med and Google Scholar	Prospective studies only	HICs	**12**
Rumrich 2016	Yes	Childhood cancers & SDP	I	All by 1 Jun. 2015	PubMed and Web of Science	Cancer patients younger than 20	Mostly HICs	**11**
Shah 2000	Yes	Preterm delivery & SDP	I	1966 to 1997	MEDLINE	English only, prospective studies only	Mostly HICs	**8**
Shobeiri 2017	Yes	Placenta previa & SDP	M	All by Jun. 2015	PubMed, Web of Science and Scopus	Not Specified	Mostly HICs	**11**
Shobeiri 2017	Yes	Placenta abruption & SDP	M	All by Ap.2016	PubMed, Web of Science and Scopus	Not Specified	Mostly HICs	**11**
Tang 2015	Yes	Autism & SDP	I	All by 10 Jun. 2015	PubMed, EMBASE, Web of Science, and Cochrane Library	Not Specified	HICs	**10**

Tsai 2017	No	Environmental pollutants and offspring health outcomes	I	All by Jan 2017	PubMed	Only studies with a birth cohort from Asian countries and published in English	UMICs	**4**
Tripathee 2016	Yes	Risks for microtia	I	January 2000 to Oct. 2014	MEDLINE, EMBASE, and Google scholar	Studies without a control group were not included, English only	Mostly HICs	**8**
Tuomisto 2009	Yes	Testicular cancer in son & SDP	I	All by January 2008	PubMed	Not Specified	Not provided	**8**
Wang 2014	Yes	Neural tube defects & SDP	I	Jan. 1, 1957 to Aug.31, 2012	PubMed, MEDLINE, Elsevier Science, and Springer Link	English studies only	Mostly HICs	**11**
Waylen 2009	Yes	Assisted reproduction & SDP	I	1806 to May 2007	Medline, Embase, Cochrane library, PsycINFO, Science Citation Index, Social Science Citation Index , CINAHL	Studies focussing on assisted reproduction were included, English only	Not provided	**10**
Wei 2015	Yes	Pre-eclampsia & SDP	M	All by Aug. 2015	PubMed and Web of Science	No information provided	HICs	**11**
Wendland 2008	Yes	Gestational diabetes & SDP	M	All by 2007	PubMed, Embase, LILACS and CINAHL	Excluded Type 1 diabetes studies	HICs	**14**
Weng 2012	Yes	Overweight & SDP	I	1990 to May 2011	MEDLINE, EMBASE, PubMed and CAB Abstracts	Children aged between two and 16, prospective studies only with at least two-year follow up	Mostly HICs	**12**
Wyszynski 1997	Yes	Oral clefts & SDP	I	Jan.1966 to Apr.1996	MEDLINE and Current Contents	Only the studies using oral clefts as cases were included.	HICs	**9**

Xuan 2016	Yes	Oral clefts & SDP	I	Jan.1966 to May 2015	Cochrane, PubMed, and Ovid Medline	Language restriction was not define but all selected studies are in English, Studies with precise information on maternal smoking were included	Not provided	**10**
Yan 2015	Yes	Childhood acute lymphoblastic leukemia	I	Not Specified	Medline, PubMed, and Web of Science	Children younger than 15, case-control studies, English only	HICs	**12**
Yermachenko 2015	Yes	Menarche age & SDP	I	1995 to 2014	PubMed, EMBASE, CINAHL, Web of Science, and Google Scholar	English, French, Russian studies	HICs	**11**
Zhang 2017	Yes	Congenital heart diseases & SDP	I	All by 24.07.2015	PubMed, EMBASE, and Web of Science	English only	Mostly HICs	**10**
Zhang 2013	Yes	SID & SDP	I	1990 to 2011	PubMed and CNKI (China National Knowledge Infrastructure)	6-criteria-item developed by the American Academy of Pediatrics Task Force was applied	Mostly HICs	**10**
Zwink 2011	Yes	Risks for anorectal malformations (ARMs)	I	All by August 2010	PubMed, EMBASE, ISI Web of Knowledge and the Cochrane Library	English only, studies reporting 2 or more ARM outcomes	HICs	**9**

Appendix 5. Health impacts of maternal SDP by study quality

Condition	Low/Moderate Quality Studies	High Quality Studies	First Author & Year
Asthma	***Aged 5-18;*** OR= 1.25 (95% CI, 1.00-1.5, n=4, I^2=55.5%)	***Aged 5-18;*** OR= 1.06 (95% CI, 0.67-1.68, n=4, I^2=76.5%)	Burke 2012
Atopic dermatitis	OR= 1.96 (95% CI, 1.50-2.64, n=UNK, I^2=UNK)	OR= 0.88 (95% CI, 0.67-1.16, n=UNK, I^2=UNK)	Kantor 2016
Autism	Studies scored ≤6 indicated a positive association OR= 1.65 (95% CI, 0.73-3.73, n=3, I^2=83.1)	Studies >6 indicated null findings OR= 1.02 (95% CI, 0.92-1.12, n=12, I^2=60.4)	Rosen 2015 Tang 2015
LBW	OR= 2.16 (95% CI, 1.68–2.77, n=14, I^2=63.3%)	OR= 1.94 (95% CI, 1.68–2.24, n=16, I^2=69.6%)	Pereira 2017
Menarche age	***All studies*** -0.092 year (95%CI, -0.160, -0.024, n=13, I^2=UNK)	***High quality studies only*** −0.116 year (95% CI,−0.214, −0.017, n=UNK)	Yermachenko 2015
Middle ear disease	OR= 0.74 (0.24-2.27, n=2)	OR= 1.17 (95% CI, 0.95-1.44, n=4)	Jones 2012
Miscarriage	OR= 1.23 (95% CI, 1.15-1.31, n=39)	OR= 1.28 (95% CI, 1.15-1.41, n=11)	Pineles 2014
Overweight & obesity	***All studies*** ***Overweight*** OR=1.07 (95% CI, 1.00-1.16, n=8, I^2=0.00%) ***Obesity*** OR= 1.23 (95% CI, 1.10-1.38, n=6, I^2=32.47%)	***High quality studies only*** ***Overweight*** OR= 1.35 (95% CI, 1.15-1.58, n=4, I^2=0.00%) ***Obesity*** OR= 1.75 (95% CI, 1.10-2.80, n=2, I^2=66.02%)	Reidel 2014
Perinatal death	**Studies with highest risk of bias** OR= 1.34 (95% CI, 1.23-1.45, n=17, I^2=UNK)	**Studies with lowest risk of bias** OR= 1.24 (95% CI, 1.18-1.30, n=2, I^2=UNK)	Pineles 2016
Placenta previa	OR= 1.4 (95% CI, 0.7-2.9, n=2, I^2=UNK)	OR= 1.6 (95% CI, 1.5-1.8, n=5, I^2=UNK)	Faiz 2003
Pre-eclampsia	OR= 0.70 (95% CI, 0.67-0.72, n= 17) RR= 0.66 (95% CI, 0.58–0.75, n=8, I^2=64.9%)	OR= 0.67 (95% CI, 0.66-0.70, n=10) RR= 0.67 (95% CI, 0.58–0.79, n=9, I^2=95.0%)	Conde-Agudelo 1999 Wei 2015
Stillbirth	OR= 1.49 (95% CI, 1.33-1.67, n=11, I^2=UNK)	OR= 1.41 (95% CI, 1.28-1.55, n=14, I^2=UNK)	Marufu 2015
Wheezing	***Aged 2 or younger;*** OR= 1.66 (95% CI, 0.93–2.96, n=5, I2 = 87.7%) ***Aged 3-4;*** OR= 1.35 (95% CI, 1.13-1.62, n= 5, I^2=72.6%)	***Aged 2 or younger;*** OR= 1.35 (95% CI, 1.13–1.61, n=9, I^2=85.3%) ***Aged 3-4;*** OR= 1.44 (95% CI, 0.92-2.25, n= 3, I^2=59.5%)	Burke 2012

Appendix 6 Health impacts of SDP by study design

Condition	Cohort Studies	Case-Control Studies	First Author & Year
Abruptio placenta	OR= 2.0 (95% CI, 1.8, 2.1, ,n=6, Q=27.5)	OR= 1.7 (95% CI, 1.6-1.9, n=7, Q=5.0)	Ananth 1999
Atopic dermatitis	OR= 0.93 (95% CI, 0.65-1.34, n= UNK, I^2=UNK)	OR= 1.14 (95% CI, 0.79-1.65, n=UNK, I^2=UNK)	Kantor 2016
Autism	OR=1.05 (95% CI, 0.88-1.25, n=6, I^2=68.9%) ***Cohort only*** OR= 0.99 (95% CI, 0.81–1.20, n=3, I^2=85%)	OR= 1.01 (95% CI, 0.88-1.15, n=9, I^2= 70%) ***Case-control or cohort*** OR= 1.03 (95% CI, 0.93–1.14, n=13, I^2=64%)	Tang 2015 Rosen 2015
Breast cancer in females	OR= 0.59 (95% CI, 0.41-0.85, n=UNK, I^2=UNK)	OR= 1.3 (95% CI, 0.93-1.15, n=UNK, I^2=UNK)	Park 2008
Brain tumors	RR= 1.07 (95% CI, 0.72–1.58, n=2, I^2=59.0%)	RR= 0.92 (95% CI, 0.84–1.00, n=14, I^2=3.1%)	Huang 2014
Congenital heart diseases	RR= 1.13 (95% CI, 0.98, 1.29, n=4, I^2=79.2%)	RR=1.11 (95% CI, 1.03-1.2, n=19, I^2=67.5%)	Zhang 2017
LBW	***Prospective cohort*** OR= 1.81 (95% CI, 1.38–2.37, n=4, I^2=50.6%) ***Retrospective cohort*** OR= 1.98 (95% CI, 1.70–2.31, n=9, I^2=58.8%)	OR= 2.07 (95% CI, 1.66–2.59, n=17, I^2= 69.5%)	Pereira 2017
Lymphoma	OR= 1.13 (95% CI, 0.92-1.38, n=3, , I^2<0)	OR= 1.32 (95% CI, 0.95-1.85, n=3, I^2<0)	Rumrich 2016
Menarche age	-0.094 (95% CI, -0.203- -0.014, n=9, I^2=UNK)	***Cross-sectional*** -0.086 (95% CI, -0.225- -0.054, n=4, I^2=UNK)	Yermachenko 2015
Middle ear disease	OR= 1.14 (95% CI, 0.84-1.53, n=5, I^2=82%)	***Cross-sectional*** OR= 1.07 (95% CI, 0.97-1.18,n=1)	Jones 2012
Miscarriage	***Cohort*** OR= 1.39 (95% CI, 1.22-1.59, n=38)	***Other studies*** OR=1.17 (95% CI, 1.11-1.24, n=22)	Pineles 2014
Oral clefts	RRs ranged between 1 to 1.17 in 10 cohort studies	RRs ranged between 1.3 and 2.3 in 22 case-control and	Little 2004
Perinatal death	OR= 1.33 (95% CI, 1.25-1.42, n=43, I^2=UNK)	OR= 1.40 (95% CI, 1.33-1.48, n=4, I^2=UNK)	Pineles 2016
Placenta previa	OR= 1.2 (95% CI, 0.9-1.5, n=1)	OR= 1.7 (95% CI, 1.5-1.9, n=8 I^2=UNK)	Faiz 2003
Pre-eclampsia	OR= 0.68 (95% CI, 0.67-0.69, n=28, I^2=59.58)	OR= 0.68 (95% CI, 0.57-0.81, n=7, I^2=5.89)	Conde-Agudelo 1999
Stillbirth	OR=1.49 (95% CI, 1.35-1.64, n= 15, I^2=84%)	OR= 1.34 (95% CI, 1.23-1.45, n=8, I^2=20%)	Marufu 2015

Appendix 7. Health impacts of SDP by sample size

Condition	Studies with Small Sample	Studies with Large Sample	First Author & Year
Atopic dermatitis	**<5000** OR= 1.37 (95% CI, 0.94-1.95, n=UNK, I^2= UNK)	**≥5000** OR= 0.77 (95% CI, 0.58-0.93, n=UNK, I^2= UNK)	Kantor 2016
Brain tumors	**≤300** RR= 1.02 (95% CI, 0.83–1.25, n=9, I^2=16.1%)	**>300** RR= 0.94 (95% CI, 0.83–1.06, n=7, I^2=42.2%)	Huang 2014
Central nervous system tumors	**Number of exposed cases<50** OR= 1.34 (95% CI, 1.06, 1.68, n=9, I^2<0)	**Number of exposed cases <100** OR= 1.05 (95% CI, 0.90, 1.22, n=7, I^2=0.4) Number of exposed cases **<150** OR= 1.09 (95% CI, 0.93, 1.28, n=3, I^2= 0.3)	Rumrich 2014
Germ cell tumors	**Number of exposed cases <50** OR= 0.67 (95% CI, 0.44, 1.00, n=2, I^2=0.1%)	**Number of exposed cases <100** OR=1.10 (95% CI, 0.87, 1.40, n=2, I^2=0.5%)	Rumrich 2014
LBW	**<1000** OR= 2.10 (95% CI, 1.54–2.87, n=16, I^2=73.1%)	**≥1000** OR= 1.94 (95% CI, 1.74–2.16, n=14, I^2=54.1%)	Pereira 2017
Leukaemia	**Number of exposed cases <50** OR= 1.07 (95% CI, 0.77-1.50, n=7, I^2=0.5)	**Number of exposed cases <100** OR= 0.91 (95% CI, 0.78-1.07, n=8, I^2=0.4) Number of exposed cases <200 OR= 0.81 (95% CI, 0.59-1.11, n=3, I^2= 0.7)	Rumrich 2014
Lymphoma	**Number of exposed cases <50** OR=1.15 (95% CI, 0.84, 1.58, n=3, I^2<0)	**Number of exposed cases <100** OR= 1.23 (95% CI, 0.96, 1.58, n=3, I^2<0)	Rumrich 2014
Neuroblastoma	**Number of exposed cases <50** OR= 1.48 (95% CI, 0.85-2.58, n=2, I^2<0)	**Overall** OR= 1.32 (95% CI, 1.01-1.74, n=5, I^2<0)	Rumrich 2014
Pre-eclampsia	**<200** OR= 0.65 (95% CI, 0.57-0.75, n=10, I^2= UNK) **< 20000** RR= 0.72 (95% CI, 0.66–0.79, n=8, I^2=0%)	**≥200** OR= 0.68 (95% CI, 0.67-0.70, n=17, I^2= UNK) **≥ 20000** RR= 0.64 (95% CI, 0.55–0.74, n=9, I^2=95.7%)	Conde-Agudelo 1999 Wei 2015
Soft tissue tumors	**Number of exposed cases <50** OR= 0.80 (95% CI, 0.58, 1.10, n=4, I^2<0)	**Overall** OR= 0.89 (95% CI, 0.71, 1.12, n=5, I^2<0)	Rumrich 2014

Appendix 8: Corrections to ESIP

1- Combined costs (mother lifetime + offspring childhood): maternal WP cost and intervention cost were double counted. This was corrected.

2- Combined costs (mother lifetime + offspring lifetime): maternal WP cost and intervention cost were double counted. This was corrected.

3- Cost of death: It was not included in the mother lifetime and offspring adulthood components. This was corrected by including the cost of death in those components.

4- Adjustment for competing risks: Starting with age 75 males with no morbidity was getting figures below zero. To avoid this adjustment of competing risks was done.

5- Health utilities: Some individuals were assigned utilities above 1 because the model used the most adjusted estimations of Maheswaran et al. (2013) which reported a constant value of 1.057. That was corrected by using the other figures reported by Maheswaran et al. (2013).

Appendix 9: HRG codes used to identify relevant NHS reference costs for maternal healthcare costs

Condition/Treatment	HRG code	Currency Description
		Antenatal care
Midwife visit	N01A	Community Midwife, Ante Natal Visit
Standard ultrasound scan	NZ21Z	Ante-natal Standard Ultrasound Scan
Specialised ultrasound scan	NZ22Z	Ante-natal Specialised Ultrasound Scan
Obstetrician	WF01A	Non-Admitted Face to Face Attendance, Follow-up
	WF01B	Non-Admitted Face to Face Attendance, First
	WF01C	Non-Admitted Non-Face to Face Attendance, Follow-up
	WF01D	Non-Admitted Non-Face to Face Attendance, First
	WF02A	Multiprofessional Non-Admitted Face to Face Attendance, Follow-up
	WF02B	Multiprofessional Non-Admitted Face to Face Attendance, First
	WF02C	Multiprofessional Non-Admitted Non Face to Face Attendance, Follow-up
	WF02D	Multiprofessional Non-Admitted Non Face to Face Attendance, First
		Maternal morbidity treatment
Ectopic pregnancy	MB08A	Threatened or Spontaneous Miscarriage, with Interventions
	MB08B	Threatened or Spontaneous Miscarriage, without Interventions
Miscarriage	MB08A	Threatened or Spontaneous Miscarriage, with Interventions
	MB08B	Threatened or Spontaneous Miscarriage, without Interventions
Placenta abruption	NZ18A	Ante-Natal Complex Disorders with CC Score 2+
	NZ18B	Ante-Natal Complex Disorders with CC Score 0-1
Placenta previa	NZ18A	Ante-Natal Complex Disorders with CC Score 2+
	NZ18B	Ante-Natal Complex Disorders with CC Score 0-1
Pre-eclampsia	NZ18A	Ante-Natal Complex Disorders with CC Score 2+
	NZ18B	Ante-Natal Complex Disorders with CC Score 0-1
	NZ19A	Ante-Natal Major Disorders with CC Score 2+
	NZ19B	Ante-Natal Major Disorders with CC Score 0-1
Premature birth	NZ25Z	Labour without Specified Delivery
		Maternal delivery
Emergency Caesarean Section	NZ51A	Emergency Caesarean Section with CC Score 4+
	NZ51B	Emergency Caesarean Section with CC Score 2-3
	NZ51C	Emergency Caesarean Section with CC Score 0-1
Caesarean Section	NZ50A	Planned Caesarean Section with CC Score 4+
	NZ50B	Planned Caesarean Section with CC Score 2-3
	NZ50C	Planned Caesarean Section with CC Score 0-1
	NZ51A	Emergency Caesarean Section with CC Score 4+
	NZ51B	Emergency Caesarean Section with CC Score 2-3
	NZ51C	Emergency Caesarean Section with CC Score 0-1
Normal Birth	NZ30A	Normal Delivery with CC Score 2+
	NZ30B	Normal Delivery with CC Score 1
	NZ30C	Normal Delivery with CC Score 0
	NZ31A	Normal Delivery, with Epidural or Induction, with CC Score 2+
	NZ31B	Normal Delivery, with Epidural or Induction, with CC Score 1

	NZ31C	Normal Delivery, with Epidural or Induction, with CC Score 0
	NZ32A	Normal Delivery, with Epidural and Induction, or with Post-Partum Surgical Intervention, with CC Score 2+
	NZ32B	Normal Delivery, with Epidural and Induction, or with Post-Partum Surgical Intervention, with CC Score 1
	NZ32C	Normal Delivery, with Epidural and Induction, or with Post-Partum Surgical Intervention, with CC Score 0
	NZ33A	Normal Delivery, with Epidural or Induction, and with Post-Partum Surgical Intervention, with CC Score 2+
	NZ33B	Normal Delivery, with Epidural or Induction, and with Post-Partum Surgical Intervention, with CC Score 1
	NZ33C	Normal Delivery, with Epidural or Induction, and with Post-Partum Surgical Intervention, with CC Score 0
	NZ34A	Normal Delivery, with Epidural, Induction and Post-Partum Surgical Intervention, with CC Score 2+
	NZ34B	Normal Delivery, with Epidural, Induction and Post-Partum Surgical Intervention, with CC Score 1
	NZ34C	Normal Delivery, with Epidural, Induction and Post-Partum Surgical Intervention, with CC Score 0
	NZ40A	Assisted Delivery with CC Score 2+
	NZ40B	Assisted Delivery with CC Score 1
	NZ40C	Assisted Delivery with CC Score 0
	NZ41A	Assisted Delivery, with Epidural or Induction, with CC Score 2+
	NZ41B	Assisted Delivery, with Epidural or Induction, with CC Score 1
	NZ41C	Assisted Delivery, with Epidural or Induction, with CC Score 0
	NZ42A	Assisted Delivery, with Epidural and Induction, or with Post-Partum Surgical Intervention, with CC Score 2+
	NZ42B	Assisted Delivery, with Epidural and Induction, or with Post-Partum Surgical Intervention, with CC Score 1
	NZ42C	Assisted Delivery, with Epidural and Induction, or with Post-Partum Surgical Intervention, with CC Score 0
	NZ43A	Assisted Delivery, with Epidural or Induction, and with Post-Partum Surgical Intervention, with CC Score 2+
	NZ43B	Assisted Delivery, with Epidural or Induction, and with Post-Partum Surgical Intervention, with CC Score 1
	NZ43C	Assisted Delivery, with Epidural or Induction, and with Post-Partum Surgical Intervention, with CC Score 0
	NZ44A	Assisted Delivery, with Epidural, Induction and Post-Partum Surgical Intervention, with CC Score 2+
	NZ44B	Assisted Delivery, with Epidural, Induction and Post-Partum Surgical Intervention, with CC Score 1
	NZ44C	Assisted Delivery, with Epidural, Induction and Post-Partum Surgical Intervention, with CC Score 0
	NZ50A	Planned Caesarean Section with CC Score 4+
	NZ50B	Planned Caesarean Section with CC Score 2-3
	NZ50C	Planned Caesarean Section with CC Score 0-1
	NZ51A	Emergency Caesarean Section with CC Score 4+
	NZ51B	Emergency Caesarean Section with CC Score 2-3
	NZ51C	Emergency Caesarean Section with CC Score 0-1
		Other maternal healthcare
Routine observation	NZ16Z	Ante-natal Routine Observation
Death	EB05A	Cardiac Arrest with CC Score 9+
	EB05B	Cardiac Arrest with CC Score 5-8
	EB05C	Cardiac Arrest with CC Score 0-4

Appendix 10: HRG codes used to identify relevant NHS reference costs for infant healthcare costs

Conditions		*Infant morbidity treatment*
Stillbirth	PB04A	Neonatal Diagnoses (Admitted from Other Location or Born in Hospital), with CC Score 6+
	PB04B	Neonatal Diagnoses (Admitted from Other Location or Born in Hospital), with CC Score 4-5
	PB04C	Neonatal Diagnoses (Admitted from Other Location or Born in Hospital), with CC Score 1-3
	PB04D	Neonatal Diagnoses (Admitted from Other Location or Born in Hospital), with CC Score 0
	PB05A	Neonatal Diagnoses (Admitted from Other Hospital Provider), with CC Score 6+
	PB05B	Neonatal Diagnoses (Admitted from Other Hospital Provider), with CC Score 1-5
	PB05C	Neonatal Diagnoses (Admitted from Other Hospital Provider), with CC Score 0
	PB06A	Neonatal Diagnoses (Admitted from Home), with Interventions, with CC Score 6+
	PB06B	Neonatal Diagnoses (Admitted from Home), with Interventions, with CC Score 4-5
	PB06C	Neonatal Diagnoses (Admitted from Home), with Interventions, with CC Score 3
	PB06D	Neonatal Diagnoses (Admitted from Home), with Interventions, with CC Score 2
	PB06E	Neonatal Diagnoses (Admitted from Home), with Interventions, with CC Score 1
	PB06F	Neonatal Diagnoses (Admitted from Home), with Interventions, with CC Score 0
	PB06G	Neonatal Diagnoses (Admitted from Home), without Interventions, with CC Score 6+
	PB06H	Neonatal Diagnoses (Admitted from Home), without Interventions, with CC Score 4-5
	PB06J	Neonatal Diagnoses (Admitted from Home), without Interventions, with CC Score 3
	PB06K	Neonatal Diagnoses (Admitted from Home), without Interventions, with CC Score 2
	PB06L	Neonatal Diagnoses (Admitted from Home), without Interventions, with CC Score 1
	PB06M	Neonatal Diagnoses (Admitted from Home), without Interventions, with CC Score 0
Neonatal care	XA01Z	Neonatal Critical Care, Intensive Care
	XA02Z	Neonatal Critical Care, High Dependency
	XA03Z	Neonatal Critical Care, Special Care, without External Carer
	XA04Z	Neonatal Critical Care, Special Care, with External Carer
	XA05Z	Neonatal Critical Care, Normal Care

Appendix 11: Prevalence of CHD, COPD, Stroke and LC amongst never smokers not exposed to SHS

	CHD				COPD				Stroke				LC			
	Female		Male		Female		Male		Female		Male		Female		Male	
Age	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
0-4	0	0	0	0	0.0001	0.0000	0.0000	0.0000	0	0	0	0	0.0000	0.0000	0.0000	0.0000
5-9	0	0	0	0	0.0001	0.0000	0.0001	0.0000	0	0	0	0	0.0000	0.0000	0.0000	0.0000
10-14	0	0	0	0	0.0002	0.0000	0.0002	0.0000	0	0	0	0	0.0000	0.0000	0.0000	0.0000
15	0	0	0	0	0.0003	0.0000	0.0003	0.0000	0	0	0	0	0.0000	0.0000	0.0000	0.0000
16-20	0.0013	0.0005	0.0010	0.0005	0.0003	0.0000	0.0003	0.0000	0.0019	0.0007	0.0016	0.0006	0.0000	0.0000	0.0000	0.0000
20-24	0.0013	0.0005	0.0010	0.0005	0.0001	0.0000	0.0003	0.0000	0.0019	0.0007	0.0016	0.0006	0.0000	0.0000	0.0000	0.0000
25-29	0.0043	0.0010	0.0016	0.0006	0.0002	0.0000	0.0003	0.0000	0.0034	0.0009	0.0037	0.0009	0.0001	0.0001	0.0001	0.0000
30-34	0.0043	0.0010	0.0016	0.0006	0.0003	0.0000	0.0005	0.0001	0.0034	0.0009	0.0037	0.0009	0.0001	0.0001	0.0001	0.0000
35-39	0.0047	0.0010	0.0063	0.0012	0.0004	0.0000	0.0004	0.0000	0.0008	0.0004	0.0039	0.0010	0.0000	0.0000	0.0000	0.0000
40-44	0.0047	0.0010	0.0063	0.0012	0.0010	0.0001	0.0010	0.0001	0.0009	0.0004	0.0038	0.0010	0.0000	0.0000	0.0000	0.0000
45-49	0.0088	0.0014	0.0168	0.0020	0.0024	0.0002	0.0022	0.0002	0.0097	0.0015	0.0106	0.0016	0.0004	0.0001	0.0003	0.0001
50-54	0.0086	0.0014	0.0180	0.0020	0.0051	0.0005	0.0022	0.0002	0.0097	0.0015	0.0106	0.0016	0.0004	0.0001	0.0004	0.0001
55-59	0.0290	0.0025	0.0180	0.0020	0.0057	0.0006	0.0045	0.0004	0.0178	0.0020	0.0289	0.0026	0.0003	0.0001	0.0002	0.0001
60-64	0.0313	0.0026	0.0575	0.0036	0.0096	0.0010	0.0048	0.0005	0.0178	0.0020	0.0289	0.0026	0.0003	0.0001	0.0003	0.0001
65-69	0.0529	0.0034	0.0988	0.0046	0.0045	0.0005	0.0080	0.0008	0.0347	0.0028	0.0551	0.0035	0.0006	0.0001	0.0006	0.0001
70-74	0.0529	0.0034	0.0988	0.0046	0.0055	0.0006	0.0108	0.0011	0.0347	0.0028	0.0549	0.0035	0.0007	0.0002	0.0008	0.0001
75-79	0.1342	0.0051	0.2036	0.0062	0.0127	0.0013	0.0160	0.0016	0.0819	0.0041	0.1019	0.0047	0.0008	0.0002	0.0009	0.0001
80-84	0.1342	0.0051	0.2036	0.0062	0.0127	0.0013	0.0180	0.0018	0.0819	0.0041	0.1019	0.0047	0.0007	0.0001	0.0008	0.0001
85+	0.1342	0.0051	0.2036	0.0062	0.0099	0.0010	0.0168	0.0017	0.0819	0.0041	0.1019	0.0047	0.0004	0.0001	0.0005	0.0001

Appendix 12: Relative risks for lifetime morbidities used in lifetime models

		CHD	COPD	Stroke	LC
Female (35-54)	Former	2.23(1.79-2.67)	1.85(1.49-2.21)	1(0.8-1.2)	2.64(2.12-3.16)
	SHS-exposed	1.24 (1.15-1.34)	1.26 (1.02-1.55)	1.25 (1.12-1.38)	1.22 (1.14-1.31)
	Current	3.88(3.12-4.64)	6.43(5.17-7.69)	2.4(1.93-2.87)	13.30(10.69-15.91)
	LS	2.57(2.15-3.00)	2.44(2.10-2.71)	1.7(1.47-2.9)	5.18(3.93-6.56)
	MS	2.89(2.43-3.31)	5.24(4.14-6.40)	1.87(1.59-2.13)	10.44(8.3-12.62)
	HS	4.66(3.68-5.66)	8.02(6.45-9.59)	2.81(2.20-3.45)	1.71(13.53-19.84)
Male 35-54)	Former	1.83(1.47-2.19)	2.22(1.78-2.66)	1.07(0.86-1.28)	4.4 (3.54-5.26)
	SHS-exposed	1.22(1.10-1.35)	1.26 (1.02-1.55)	1.25 (1.12-1.38)	1.14(1.01-1.29)
	Current	4.98(4-5.96)	4.5(3.6-5.3)	2.44(1.96-2.92)	14.3(11.5-17.1)
	LS	3.88 (3.03-4.78)	1.57(1.36-1.75)	1.98(1.59-2.36)	5.66(4.43-6.98)
	MS	4.14 (3.24-5.09)	3.38(2.66-4.13)	2.06(1.66-2.45)	10.17(7.92-12.58)
	HS	5.35(4.33-6.34)	5.17(4.16-6.18)	2.60(2.09-3.11)	16.64(13.46-19.77)
Female (55-64)	Former	1.21(0.97-1.45)	4.84(3.79-5.79)	1.1(0.88-1.32)	5(4.02-5.98)
	SHS-exposed	1.24 (1.15-1.34)	1.26 (1.02-1.55)	1.25 (1.12-1.38)	1.22 (1.14-1.31)
	Current	3(2.4-3.58)	9(7.24-10.76)	2.51(2.02-3)	18.95(15.24-22.66)
	LS	2.54(2.07-2.77)	4.92(4.22-5.51)	2.2(1.83-2.55)	10.72(8.22-13.35)
	MS	2.85(2.34-3.34)	10.58(8.26-13.02)	2.42(1.98-2.85)	21.59(17.45-25.68)
	HS	4.59(3.54-5.71)	16.18(12.91-19.5)	3.63(2.74-4.62)	34.57(28.44-40.39)
Male (55-64)	Former	1.52(1.22-1.82)	3.98(3.2-4.76)	1.51(1.21-1.81)	4.57(3.67-5.47)
	SHS-exposed	1.22(1.10-1.35)	1.26 (1.02-1.55)	1.25 (1.12-1.38)	1.14 (1.01-1.29)
	Current	3.25(2.61-3.89)	15.2(12.2-18.1)	1.98(1.59-2.37)	19(15.3-22.8)
	LS	3.67 (2.91-4.44)	9.26 (7.99-10.28)	2.29(1.84-2.74)	13.17(10.47-15.94)
	MS	3.92 (3.12-4.73)	19.90 (15.64-24.32)	2.38(1.92-2.84)	23.66(18.72-28.75)
	HS	5.05 (4.17-5.89)	30.44 (24.46-36.42)	3.01(2.41-3.62)	38.7(31.83-45.18)
Female (65-74)	Former	1.56(1.25-1.87)	15.72(12.64-18.8)	1.24(1-1.48)	6.8(5.47-8.13)
	SHS-exposed	1.24 (1.15-1.34)	1.26 (1.02-1.55)	1.25 (1.12-1.38)	1.22 (1.14-1.31)
	Current	2.8(2.22-3.3)	38.89(31.27-46.51)	2.17(1.74-2.60)	23.65(19.01-28.29)
	LS	2.34(1.91-2.11)	21.27(18.21-23.4)	1.91(1.58-2.21)	13.38(10.31-16.67)
	MS	2.63(2.16-3.08)	45.71(35.67-56.28)	2.09(1.71-2.47)	29.65(21.77-32.06)
	HS	4.24(3.27-5.27)	69.93(55.77-84.29)	3.14(2.37-3.99)	43.15(35.48-50.42)
Male (65-74)	Former	1.58(1.27-1.89)	8.13(6.54-9.72)	1.23(0.99-1.47)	7.79(6.26-9.32)
	SHS-exposed	1.22(1.10-1.35)	1.26 (1.02-1.55)	1.25 (1.12-1.38)	1.14 (1.01-1.29)
	Current	3.29 (2.65-3.93)	29.7(23.7-35.5)	2.27(1.83-2.71)	28.3(22.7-33.8)
	LS	3.71 (2.95-4.5)	18.12(15.63-20.12)	2.63(2.11-3.14)	19.57(15.56-23.7)
	MS	3.96 (3.15-4.79)	38.95(30.62-47.60)	2.73 (2.2-3.26)	35.17(27.83-47.73)
	HS	5.12 (4.22-5.96)	59.58(47.87-71.28)	3.45(2.76-4.15)	57.54(47.32-67.17)
Female (75+)	Former	1.27(1.02-1.52)	7.06(5.68-8.44)	1.1(0.88-1.32)	6.38(5.13-7.63)
	SHS-exposed	1.24 (1.15-1.34)	1.26 (1.02-1.55)	1.25 (1.12-1.38)	1.22 (1.14-1.31)
	Current	2(1.59-2.37)	20.96(16.85-25.07)	1.48(1.19-1.77)	23.08(18.56-27.06)
	LS	1.68(1.37-1.98)	11.47(9.81-12.83)	1.3(1.08-1.5)	13.06(10.07-16.26)
	MS	1.89(1.55-2.21)	24.64(19.22-30.34)	1.43(1.16-1.68)	26.29(21.25-31.28)
	HS	3.04(2.35-3.78)	37.69(30.05-45.43)	2.14(1.61-2.72)	42.11(34.64-49.19)
Male (75+)	Former	1.32(1.06-1.58)	6.55(5.27-7.83)	1.12(0.9-1.34)	6.46(5.19-7.73)
	SHS-exposed	1.22(1.10-1.35)	1.26 (1.02-1.55)	1.25 (1.12-1.38)	1.14 (1.01-1.29)
	Current	2.25(1.81-2.69)	23(18.5-27.5)	1.7(1.37-2.03)	22.5(18.1-26.9)
	LS	2.54 (2.02-3.07)	14.05 (12.12-15.6)	1.97(1.58-2.35)	15.57(12.38-18.86)
	MS	2.71 (2.16-3.27)	30.18 (23.73-36.89)	2.05(1.65-2.44)	27.98(22.15-34)
	HS	3.50 (2.89-4.08)	46.17 (37.10-55.24)	2.58(2.07-3.1)	45.78(37.65-53.45)

Appendix 13: Probability of SID based on birth weight

	Number of SID		Number of birth		Probability	
Birth weight	**Under 2,500g**	**2500g +**	**Under 2,500g**	**2500g +**	**Under 2,500g**	**2500g +**
2004	90	227	48,178	584,887	0.0019	0.00039
2005	96	227	48,255	602,286	0.0020	0.00038
2006	72	209	50,037	610,119	0.0014	0.00034
2007	60	208	49,180	636,564	0.0012	0.00033
2008	73	211	50,445	651,905	0.0014	0.00032
2009	85	196	50,267	657,664	0.0017	0.00030
2010	63	192	50,325	672,667	0.0013	0.00029
2011	51	190	50,970	665,355	0.0010	0.00029
2012	44	189	51,122	676,011	0.0009	0.00028
2013	51	198	49,072	649,841	0.0010	0.00030
2014	42	163	48,419	629,699	0.0009	0.00026
2015	54	134	48,656	638,638	0.0011	0.00021
2016	60	150	48,648	639,858	0.0012	0.00023
Mean	65	192	49,506	639,653	**0.0013**	**0.0003**

Source: ONS (2016), unexplained deaths in infancy, Table 5.

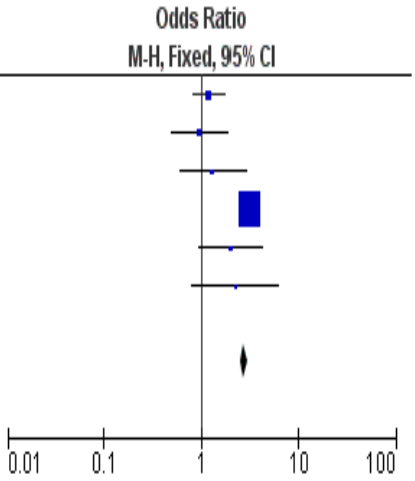
Appendix 14: Estimating SID ORs based on severity of smoking

Estimating SID ORs amongst children of light or moderate smokers compared to never smokers

	Events		Control			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Dalveit 2003	46	247	135	850	11.5%	1.21 [0.84, 1.75]
Froen 2002	11	65	92	529	3.9%	0.97 [0.49, 1.92]
l'Hoir 1998	12	73	19	146	2.5%	1.31 [0.60, 2.88]
Pollack 2001	574	2516	258924	2962512	79.1%	3.09 [2.81, 3.39]
Schellscheidt 1997	14	59	21	156	2.1%	2.00 [0.94, 4.26]
Wisborg 2000	5	20	3244	24966	0.9%	2.23 [0.81, 6.15]
Total (95% CI)		**2980**		**2989159**	**100.0%**	**2.71 [2.48, 2.97]**
Total events	662		262435			

Heterogeneity: Chi² = 38.33, df = 5 (P < 0.00001); I² = 87%

Test for overall effect: Z = 21.93 (P < 0.00001)

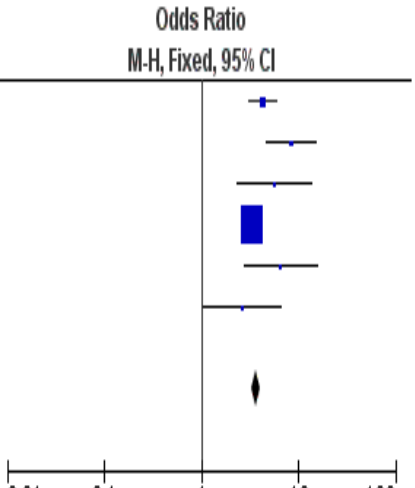


Estimating SID ORs amongst children of heavy smokers compared to never smokers

	Events		Control			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Dalveit 2003	96	247	109	850	12.2%	4.32 [3.12, 5.98]
Froen 2002	27	65	41	529	2.1%	8.46 [4.70, 15.22]
l'Hoir 1998	18	73	8	146	1.6%	5.65 [2.32, 13.74]
Pollack 2001	352	2516	136572	2962512	80.9%	3.37 [3.01, 3.77]
Schellscheidt 1997	17	59	9	156	1.4%	6.61 [2.75, 15.90]
Wisborg 2000	7	20	4194	24966	1.8%	2.67 [1.06, 6.69]
Total (95% CI)		**2980**		**2989159**	**100.0%**	**3.66 [3.31, 4.06]**
Total events	517		140933			

Heterogeneity: Chi² = 14.05, df = 5 (P = 0.02); I² = 64%

Test for overall effect: Z = 24.88 (P < 0.00001)



Appendix 15: HRG Currency codes used to estimate the cost of lower respiratory illness

HRG code	Description
DZ11K	Lobar, Atypical or Viral Pneumonia, with Multiple Interventions, with CC Score 14+
DZ11L	Lobar, Atypical or Viral Pneumonia, with Multiple Interventions, with CC Score 9-13
DZ11M	Lobar, Atypical or Viral Pneumonia, with Multiple Interventions, with CC Score 0-8
DZ11N	Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 13+
DZ11P	Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 8-12
DZ11Q	Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 0-7
DZ11R	Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 14+
DZ11S	Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 10-13
DZ11T	Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 7-9
DZ11U	Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 4-6
DZ11V	Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 0-3
DZ22K	Unspecified Acute Lower Respiratory Infection with Interventions, with CC Score 9+
DZ22L	Unspecified Acute Lower Respiratory Infection with Interventions, with CC Score 0-8
DZ22M	Unspecified Acute Lower Respiratory Infection without Interventions, with CC Score 13+
DZ22N	Unspecified Acute Lower Respiratory Infection without Interventions, with CC Score 9-12
DZ22P	Unspecified Acute Lower Respiratory Infection without Interventions, with CC Score 5-8
DZ22Q	Unspecified Acute Lower Respiratory Infection without Interventions, with CC Score 0-4
PD14A	Paediatric Lower Respiratory Tract Disorders without Acute Bronchiolitis, with CC Score 11+
PD14B	Paediatric Lower Respiratory Tract Disorders without Acute Bronchiolitis, with CC Score 8-10
PD14C	Paediatric Lower Respiratory Tract Disorders without Acute Bronchiolitis, with CC Score 4-7
PD14D	Paediatric Lower Respiratory Tract Disorders without Acute Bronchiolitis, with CC Score 2-3
PD14E	Paediatric Lower Respiratory Tract Disorders without Acute Bronchiolitis, with CC Score 0
PD15A	Paediatric Acute Bronchiolitis with CC Score 5+
PD15B	Paediatric Acute Bronchiolitis with CC Score 2-4
PD15C	Paediatric Acute Bronchiolitis with CC Score 1
PD15D	Paediatric Acute Bronchiolitis with CC Score 0
Source: 2017-2018 NHS Reference Costs	

Appendix 16: Distributions used in the probabilistic sensitivity analysis

Parameter group	Distribution	Sampling method
Smoking behaviour (intervention vs. comparator)	Beta	Difference
Probability of being LS, MS, HS amongst smokers	Beta	Difference
Pregnancy-related morbidity probabilities	Beta	Independent
Probability of prematurity and stillbirth	Beta	Independent
Mortality probabilities	Beta	Independent
Probability of being male	Beta	Independent
Probability of SHS exposure in relation to parental smoking	Beta	Difference
Probability of starting smoking	Beta	Independent
Lifetime morbidity probabilities	Beta	Independent
SID probability in relation to parental smoking during pregnancy	Beta	Difference
Other cause infant mortality in relation to parental smoking during pregnancy	Beta	Difference
Asthma probability in relation to parental smoking during pregnancy	Beta	Difference
LRI probability in relation to parental smoking during pregnancy	Beta	Difference
RRs for starting to smoke in relation to SHS	Log Normal	Independent
ORs for asthma in relation to SHS	Log Normal	Independent
OR/RR for the remaining morbidity and mortality risks in relation to SHS, LS, MS, HS	Log Normal	Difference
Health utilities in relation to LS, MS, HS	Beta	Difference
Remaining utilities	Beta	Independent
Intervention cost in relation to SHS	Gamma	Difference
All other costs	Gamma	Independent

Appendix 17. Tailoring characteristics and examples of MiQuit text messages

(Source: Naughton et al. 2017)

14 tailoring characteristics used to individually tailor MiQuit text messages

1. Motivation to quit (seriously planning to quit within the next 2 weeks, 30 days, 3 months or not planning to quit)
2. Whether quit date has been set (date of that quit date)
3. Most difficult situation to resist smoking (socialising, first thing in the morning, when stressed, during an urge)
4. Self-efficacy/confidence to quit smoking for the remainder of pregnancy (1 – 5 scale, 1 = not at all, 5 = extremely)
5. Number of cigarettes smoked per day (from the Heaviness of Smoking Index)
6. Time to first cigarette (from the Heaviness of Smoking Index)
7. Has a partner that smokes
8. Longest previous quit attempt (less than 2 weeks, 2-5 weeks, 6-11 weeks, 12 weeks + or not previously attempted to quit)
9. Difficulty of longest previous quit attempt (1 – 5 scale, 1 = not at all, 5 = extremely)
10. Perceived main disadvantage of quitting (increased tension, weight gain, feeling dull/bored, none of these)
11. Perceived main reason for quitting, apart from for baby's health (your health, taking control, saving money, none of these)
12. Determination to quit smoking for good (1 – 5 scale, 1 = not at all, 5 = extremely)
13. Gestation
14. Smoking status at 3 and 7 weeks into programme

Example text messages

Day in delivery schedule and tailoring characteristics used for each message listed in parentheses

Motivation

(Day 7: *Quit date set but not passed, smokes 5 or less per day*)

"Even smoking [*smoking rate*] a day can have a big impact on your baby's health. So it's great news that you've picked a quit date and plan to avoid this"

(Day 19: *low motivation, most important reason for quitting is money, baseline smoking rate 11-15 per day*)

"To boost your motivation, keep reminding yourself why quitting is important to you - to have a healthy baby and an extra £30 a week to spend"

Preparation

(Day 31: *Low motivation, not set a quit date, most difficult situation is socialising*)

“If you're going to set a quit date [*name*], choose a time when you're least around other smokers e.g. if you socialise more on weekends, quit on a Monday”

(Day 33: *high motivation, most difficult situation is morning, partner smokes*)

"If you struggle to not smoke in the mornings, work on changing your morning routine, try changing the order you do things & ask others not to smoke near you"

Self-efficacy

(Day 37: *low self-efficacy, low determination to quit for good*)

“Hi [*name*] hope you're well & feeling a bit more determined to quit. You really can do this. Let yourself become more confident each time you resist smoking”

(Day 16: *Not set a quit date, longest previous quit less than 6 weeks, previous quit attempt was difficult*)

"Don't let your past quitting experience put you off trying to quit this time. Think about which situations were the hardest & make a plan to overcome them"

Outcome expectancies

(Day 57-59 depending on track: *Not abstinent at 3 weeks into programme, abstinent at 7 weeks into programme*)

"You should find your recent quit attempt got easier when you went over the 2 week point. Withdrawal symptoms should be fading & cravings to smoke less common"

(Day 18: *low motivation, main disadvantage with quitting is tension*)

"You are concerned about dealing with tension & irritability when quitting. Taking some time-out or trying mild exercise can boost your mood & help you relax"

Relapse prevention

(Day 52: *Abstinent at 3 weeks into programme, not abstinent at 7 weeks into programme*)

“What situation brought you back to smoking during your recent quit attempt? Write down some things you could do next time to help manage your cravings”

(Day 22: not tailored)

"Text QUIZ to this number if you need a brief distraction from a craving. Use QUIZ as much as you like, but it works best if you agree not to smoke when using it"

Postpartum

(Day 78: *high determination to quit long-term, abstinent at 7 weeks into programme, most difficult situation is socialising*

"You may find after giving birth that some situations are harder at first - watch out for social situations. Rehearse saying 'no thanks, I've quit'"

(Day 67-69 depending on track: *main disadvantage with quitting is weight gain*)

"You are concerned about weight gain from quitting long-term. However, weight gain

is preventable - healthy snacks between meals and keeping active works :-)"

Baby information

(Sent at 20 weeks gestation)
“Baby info: Week 20 - your baby is about the length of a banana! They are probably quite active at the moment - they can even do the occasional somersault!”

Additional support if quit date set

(Sent day before quit day)
"Tomorrow's the big day. Quitting will be tough but you can do it - we believe in you :-) Just take each day as it comes and remember - not even a puff"

HELP instant support

"Remember that cravings only usually last a few minutes at a time. Keep yourself busy or distracted and they WILL pass."

SLIP instant support

"Think about what made you light up? How could you prevent it next time? A good way can be to remind yourself why you are quitting"

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