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# Cost-Effectiveness of an E-Health Intervention to Improve Unhealthy Lifestyle Behaviors in Subfertile Women

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## Abstract

**Background**: 'Slimmer Zwanger' is an e-health tool on the smartphone developed to improve the lifestyle behaviors of couples with a child wish, in order to increase the chance of pregnancy and improve pregnancy outcomes. The aim of this study was to assess the costs-effectiveness of coaching through e-health with the 'Slimmer Zwanger' intervention in subfertile women. Decision analytic modeling was used to compare 'Slimmer Zwanger' to 'do nothing'.

**Methods**: Three models were developed and populated using survey data from the Erasmus Medical Centre and literature. The models reflected a range from intermediate to final outcomes. Outcome of model 1 is a reduction in unhealthy lifestyle behaviors, either in percentage of women achieving a complete healthy lifestyle, or a reduction in number of unhealthy lifestyle behaviors. The outcome of the second model was percentage of pregnancies achieved and of the third model percentage of healthy babies born.

Costs, effects and incremental costs effectiveness ratio's (ICER's) were calculated from a health care and a societal perspective during a one year time horizon. Probabilistic sensitivity analyses were performed and results were represented in Cost Effectiveness Acceptability Curves (CEACs).

**Results**: The percentage of women who achieved a completely healthy lifestyle was on average 3% higher when 'Slimmer Zwanger' was used than when nothing was done. In addition, women who used 'Slimmer Zwanger' had a lower number of unhealthy lifestyle behaviors. The probability that 'Slimmer Zwanger' is cost-effective compared to 'do nothing' is approximately 95% for the societal and 99% for the health care perspective, when a maximum acceptable cost effectiveness threshold of €1000 per reduction of one unheatlhy lifestyle behavior in subfertile women is used.

Approximately 3% more pregnancies are expected in subfertile women when 'Slimmer Zwanger' is used than when nothing is done, with a mean additional costs of €-67 and €-362 from health care and societal point of view respectively. The probability that 'Slimmer Zwanger' is cost-effective compared to 'do nothing' in terms of pregnancies achieved is approximately 0.65 and 0.88 with a cost-effectiveness threshold of zero, for the health care and societal perspective respectively.

Furthermore, on average 3.4% more healthy babies are expected to be born when 'Slimmer Zwanger' is used compared to 'do nothing'. Incremental costs are expected to be €-196 (health care perspective) and €-477 (societal perspective). The probability that 'Slimmer Zwanger' is cost effective compared to 'do nothing' in terms of healthy babies born is approximately 0.75 for the health care- and 0.90 for the societal perspective, with a cost-effectiveness threshold of zero.

**Conclusion**: 'Slimmer Zwanger' decreased the number of unhealthy lifestyle behaviors in subfertile women over a one year period. This resulted in a higher expected pregnancy probability and a higher expected probability of having a healthy baby. Due to high costs of fertility treatment and costs related to adverse pregnancy outcomes, and the relatively low costs of 'Slimmer Zwanger', there is a high probability that 'Slimmer Zwanger' is cost-effective compared to 'do nothing '. Moreover, there is a high probability that 'Slimmer Zwanger' is more effective and less costly compared with 'do nothing', which suggests that 'Slimmer Zwanger' is dominant over 'do nothing'.

# Background

## *Subject Introduction*

Having an unhealthy lifestyle is a prevalent problem all over the world. This is a growing concern because many chronically diseases are related to these unhealthy behaviors (Van der Lucht & Polder, 2010). In the Netherlands, more than 90% of males and females have one or several unhealthy lifestyle behaviors (Schuit et al., 2002). For instance, 22% of woman and 31% of males smoke, 74% of women and 86% men drink alcohol and 53% of men and 42% of women are obese or have overweight (Statistics Netherlands, 2010). Unhealthy lifestyle behaviors are harmful for the own health and wellbeing of individuals, but there is also growing evidence that having one or several unhealthy lifestyle behaviors has a negative effect on fertility (Homan et al., 2007). In addition, having one or several unhealthy lifestyle behaviors during pregnancy increases the risk of adverse pregnancy outcomes that can result in perinatal mortality and morbidity (Bonsel et al., 2010; Djelantink et al., 2011; Donald et al., 1999; Hackshaw et al., 2011; Vujkovic et al., 2009; Wilcox, 2001)

## *Relevance*

Problems with fertility and perinatal mortality and morbidity cause both financial and psychosocial costs. About 10-15 % of all couples in Western countries are affected by impaired fertility and there is growing evidence that part of these fertility problems are associated with modifiable unhealthy lifestyle factors (Anderson et al., 2010; Evers, 2002). In the view of this, change these unhealthy lifestyle factors during the reproductive period will contribute to the prevention of subfertility as well as the related financial and psychosocial costs.

In addition, the Netherlands has a relatively high number of perinatal mortality compared to other European countries. There are three important risk factors associated with this perinatal mortality i.e. premature birth, low birth weight and birth defects (together BIG3) (Mohangoo et al., 2008). These risk factors are also associated with modifiable lifestyle factors (Bonsel et al., 2010). This suggests that perinatal mortality and morbidity and related costs and consequences are partly preventable by increasing unhealthy lifestyle behaviors.

## *Preconception Care*

Preconception care is a preventive approach to change unhealthy lifestyle behavior during the preconception period of couples who are trying to become pregnant (Allaire & Cefalo, 1998; Hammiche et al 2011). The focus on preconception care has gained more attention, since it seems to be the best way to improve the health of parents and their children. In recent years, different forms of preconception care have been developed in the Netherlands (Health Council of the Netherlands, 2007). An example is the outpatient clinic at the Erasmus Medical Centre on preconception dietary and lifestyle counseling, that recently has been proven to be effective in reducing unhealthy lifestyle behaviors of subfertile couples (Hammiche et al., 2011; Twigt et al., 2012).

## *Intervention 'Slimmer Zwanger'*

To make preconception care accessible and to reach a large population, the Erasmus MC has developed an innovative e-health intervention 'Slimmer Zwanger'. This intervention uses the mobile phone to coach couples, who are trying to conceive or being pregnant, with personalized advices and rewards on dietary and lifestyle behaviors. Aim is to reduce the unhealthy behaviors in males and females with a child wish and improve the chance to become pregnant and reduce miscarriage and BIG3 outcomes (birth defects, premature birth and low birth weight).

The program starts with register through the web-site www.slimmerzwanger.nl . A personal screening of the woman and her partner is done with a questionnaire on the web-site. The questions are related to several lifestyle factors i.e. age, BMI, eight nutrition risk factors and five lifestyle risk factors, including exercise. The program identifies a risk-score and based on this score a customized program is developed. The couples get information about the unhealthy and healthy lifestyle habits. Through SMS and e-mail, tips, tricks, rewards and recipes are offered. Intention is to create awareness and change undesirable unhealthy behavior. The program is biannual and there are four screening moments, each six weeks after the previous screening. This allows the program to adjust to new circumstances and provide the couples with relevant coaching.

## *Objective*

Recent studies have shown that preconception counseling in an outpatient clinic is effective in reducing unhealthy lifestyle behaviors in subfertile couples. The study revealed that both women and man significantly improved their unhealthy behaviors (Hammiche et al., 2011; Twigt et al., 2012). In addition, studies have shown that the effectiveness of e-health tools aimed at improving unhealthy behavior can be quite high (Klasjna et al., 2009; Rizvi et al., 2011).

This suggests that e-health can be a good way to improve the lifestyle behaviors of both women and men before and during pregnancy. As mentioned above, there is growing evidence that subfertility and adverse pregnancy outcomes are associated with modifiable lifestyle factors of both men and women. Therefore, it is expected that through improved lifestyle of men and women, the number of pregnancies achieved in subfertile couples can increase and number of adverse pregnancy outcomes can reduce. As costs of e-health are relatively low, but costs of fertility treatment and hospital stay are high, it might be expected that through an e-health intervention that aims to modify unhealthy behaviors of subfertile couples, health care costs can be saved.

To assess whether investing in an intervention offers value for money, economic evaluations are done. A cost effective analysis is an often used type of economic evaluation in which costs and effects of an intervention and at least one alternative are calculated (Drummond et al., 2005). Previous cost-effectiveness studies of preconception care reveal positive results; however cost-effectiveness studies of preconception care are scarce and often evaluate preconception care targeted at small populations, for instance women with Diabetes Mellitus (Elixhauser et al., 1993; Herman et al., 1999; Scheffler et al., 1992). In addition, no cost-effectiveness studies exist which evaluate preconception e-health interventions.

Objective of this study was to assess the costs and effectiveness of coaching through e-health with the ‘Slimmer Zwanger‘ intervention, for subfertile women in the Netherlands aged 18-45 who try to become pregnant. Although unhealthy lifestyle behaviors of both man and women contribute to the reproductive performance, the intervention ‘Slimmer Zwanger’ is primarily offered to women. Men are only advised to participate. Therefore it was chosen to evaluate the cost-effectiveness of ‘Slimmer Zwanger’ for subfertile women only.

Since in the Netherlands no centrally organized preconception care is available (Health Council of the Netherlands, 2007), ‘do nothing’ was chosen as the relevant comparator for the cost-effectiveness analysis. The intervention was evaluated both form a health care and a societal perspective.

### *Research Questions*

Three research questions were formulated in order to accomplish the overall objective.

1. Taking a societal perspective and a health care perspective, is the e-health intervention “Slimmer Zwanger” cost-effective compared to ‘do nothing’ to reduce unhealthy lifestyle behaviors in subfertile women planning pregnancy, between the age of 18-45?
2. Taking a societal perspective and a health care perspective, is the e-health intervention “Slimmer Zwanger” cost-effective compared to ‘do nothing’ to increase pregnancy probability in subfertile women between the age of 18-45?
3. Taking a societal perspective, is the e-health intervention “Slimmer Zwanger” cost-effective compared to ‘do nothing’ to increase the percentage of healthy babies born in subfertile women (age 18-45) who do become pregnant?

### *Outline of the Thesis*

This thesis starts with a theoretical framework in which important concepts are explained in more detail. Followed by a chapter in which methods used are described. Afterwards, the results of the study are presented followed by a discussion. Finally an overall conclusion is described and interpretations for policy are given.

# Theoretical Framework

In this section, lifestyle behaviors and their association with subfertility and pregnancy outcomes are described in more detail. In addition, a description is given of economic evaluation in health care supplemented with a description of economic evaluation in public and preventive health care.

## *Lifestyle and Subfertility*

In the Western world, impaired fertility affects about 10-15% of all couples. Subfertility is defined as at least one year of unprotected intercourse without a result of pregnancy. There are several factors that can affect fertility (Evers, 2002). Previous research has shown that different lifestyle behaviors such as BMI, smoking and age, have a negative effect on fertility. Modifying these behaviors can increase the probability that couples become pregnant without a major intervention (Homan et al., 2007). In addition, the chance of ongoing pregnancy after fertility treatment is higher with a healthy diet (Twigt et al., 2012). Below, different lifestyle factors in relation to fertility are discussed.

### *Nutrition*

Nutrition has often been a neglected lifestyle factor in studies regarding fertility (Ebisch et al., 2007). However, recently more attention is paid to this lifestyle factor, especially in relation to fertility treatment. For instance, Vujkovic et al. (2010) found that adherence to a 'Mediterranean dietary pattern' of couples, with high intakes of folate and other vitamine B, increases the probability of achieving pregnancy after IVF/ICSI with 40%. Recent research adds to this, that adherence to recommendations of the Netherlands Nutrition Centre is associated with a 65% increased chance of ongoing pregnancy after fertility treatment (Twigt et al., 2012). These findings suggest that poor nutrition is associated with subfertility and using a healthy diet decreases the chance of subfertility in couples. Mechanisms underlying this are not clearly understood yet. However, Steegers-Theunissen et al. (2013) found evidence that poor nutrition related to folate and B12 contribute to subfertility. Other micronutrients such as zinc and antioxidants might play an important role in fertility as well (Ebisch et al., 2007).

Folate is present in for example fruits, whole grains and vegetables and the Mediterranean diet (Ebisch et al., 2007). In addition to the association between folate and fertility, the consumption of the synthetic derivative of folate, folic acid, in early stage of pregnancy reduces the chance of neural tube defects and other birth defects (Twigt et al., 2011; Yi et al., 2006; Wilson et al., 2003). Therefore, it is recommended to use folic acid in the periconceptional period (Health council of the Netherlands, 2003). Several countries, for instance the USA, Canada and Chile, added folate to regular food, such as grain products, in order to increase the intake of females and prevent neural tube defects (Bentley et al., 2009; Yi et al., 2011)

### *Smoking*

It is widely recognized that smoking is bad for the health of individuals. Therefore, it is not surprising that smoking is thought to be an important unhealthy lifestyle factor associated with subfertility. Several studies have shown an increase in the risk of subfertility and an increase in the time to conception in woman who smoke. In woman undergoing IVF treatment, smokers need more IVF cycles to become pregnant than non-smokers (Augood et al., 1998; Hughes et al., 1996; Hull et al., 2000). In addition, male smoking is associated with lower semen quality which is related to fertility.

Moreover, it has been shown that male smoking decreases the probability to become pregnant after IVF treatment (Joesbury et al., 1998; Ramlau-Hansen et al., 2007; Vine et al., 1994).

### *Alcohol*

Alcohol intake of females is associated with subfertility, but depends on the amount of alcohol consumed (Barbieri, 2001). Previous research suggests that even a moderate amount of alcohol consumption, a weekly intake of five drinks, might decrease fertility. Therefore, it is recommended that women who are trying to become pregnant should not consume alcohol at all (Jensen et al., 1998; Hakim, 1998). For males, heavy alcohol drinking is associated with decreased fertility, but not much is known yet about moderate alcohol consumption (Barbieri, 2001).

### *BMI*

Both, being overweighed and being underweighted, is associated with decreased fertility in woman. The risk of subfertility starts to increase with a BMI of 24, which is only modestly overweight, and increases constantly with every unit BMI. At the same time, a BMI of 20 and below increases the risk of subfertility as well (Evers, 2002). Although less research has been done about male weight in relation to fertility, there are studies that suggest that excess body weight in males also contributes to subfertility and reduced sperm quality (Hammiche et al., 2012; Nguyen et al., 2007; Sermondade et al., 2012). Since obesity an overweight tend to cluster in couples, it is interesting to know whether obesity/overweight in both couples increases the risk of infertility (Ramlau-Hansen et al., 2007). Ramlau-Hansen et al. (2007) have found higher risks of infertility in couples being overweight or obese.

### *Physical Activity*

Some studies have shown that exercise increases fertility. For instance, Rich-Edwards et al. (2002) have shown that vigorous activity, such as running, dancing and bicycling, is associated with increased fertility among woman. The mechanism, through which exercise increases fertility, has not been proven (Anderson et al., 2010). In contrast, very intensive physical training is associated with decreased fertility, which can be reversed by decreasing the amount of exercise (Roupas & Georgopoulos, 2011).

## *Lifestyle and Pregnancy Outcomes*

Having one or several unhealthy lifestyle behaviors is also associated with adverse pregnancy outcomes. Having an unhealthy lifestyle during pregnancy increases the risk of perinatal mortality and morbidity (Bonsel et al., 2010).

## *BIG3*

There are four important risk factors, that occur in 16% of the pregnancies and are associated with perinatal mortality i.e. premature birth, low birth weight, birth defects and low Apgar score, together the BIG4. Premature birth, low birth weight and birth defects together the BIG3, depend for a substantial part on risk factors, such as lifestyle, nutrition, age, stress. Especially important are those risk factors that are present during the preconception period, since these have the biggest effect on the mentioned pregnancy outcomes. Of prenatal mortality is 82% associated with BIG3 (Bonsel et al., 2010).

Pre-term birth and low birth weight are more prevalent than birth defects. Of the pregnancies in which BIG4 occurs, 16% has birth defects, 45% low birth weight, 44% premature birth and 11% lows Apgar score (Bonsel et al. 2010). Pre-term birth is defined as the birth before 37 weeks of gestation. Low birth is the weight is defined as less than 2500 grams. Birth defects are harder to define. The WHO describes birth defects as 'structural or functional anomalies, including metabolic disorders, which are present at the time of birth' (World Health Organization, 2011). Subfertile women who conceive through fertility treatment have a higher risk on premature birth, low birth weight and birth defects. In addition, conception in women who have a history of subfertility and conceive without any fertility treatment has an increased risk on birth defects compared to fertile women. Therefore, the underlying parental factors (such as their lifestyle) might play an important role in the onset of BIG3 (Davies et al., 2012).

### *E-health Tools*

Health care is constantly changing on different aspects. For instance, the types of diseases are changing and the patients attitudes towards health care are changing. Patients no longer want to be passively treated but they want to get involved in the process of care. In addition, technology is rapidly changing as is our dependency on this technology (Rizvi et al., 2011).The changes in attitudes and opportunities of new technology ask for innovation in health care. E-health might be an interesting technology to involve patients in the health care process (Van Gemert-Pijnen et al., 2011).

By definition "E-health is the transfer of health resources and health care by electronic means" (World Health Organization, 2013). One of the main areas of e-health is delivering health information for consumers. E-health can help to improve the efficiency in use of resources in health care such as information, medicine and money (World Health Organization, 2013). Previous research has shown that the effectiveness of e-health tools can be quite high and can indeed improve healthy behavior (Klasjna et al., 2009; Moore et al., 2008; Rivzi et al., 2011). However, a slow adoption of e-health in health care is seen (Wicks et al., 2013).

## *Economic Evaluation in Health Care*

There is a growing attention for economic evaluations in health care. This because resources such as time, facilities and equipment in health care are scares and insufficient to meet all demands. Therefore, decisions must be made. Making good decisions in health care is a complex task since the effects of the decisions can be immense and the decisions often involve a wide range of uncertainties. To support health care decision makers in making efficient and equitable decisions, evidence from economic evaluations can be used (Brazier et al., 2007; Hunink et al., 2001).

Economic evaluations are defined as the comparison of alternative health care interventions in terms of both their costs and consequences. Interventions can be interpreted broadly for instance as new type of medicine or things such as screenings, vaccines, technologies or health promotion programs.

Four types of economic evaluations in health care exist i.e. costs-effectiveness analysis (CEA), cost-benefit analysis (CBA), cost-utility analysis (CUA) and cost-minimization analysis (CMA). Basic tasks of all these economic evaluations are to identify, measure, value and compare the costs and consequences of the intervention and the available alternatives. The identification, measurement and valuation of various types of costs are similar across these four types of economic evaluations;

however the measurement and valuation of the consequences arising from the different alternatives which are examined are different (Drummond et al., 2005; Uyl-de Groot & Rutten-van Mölken, 2010).

In CEA costs are related to the natural units of effect. Therefore, alternatives can only be compared when they have common effects. A special type of CEA is the CUA. The CUA uses a generic outcome as the measure of effect. The most commonly used outcome measure is the QALY, 'quality adjusted life years'. The QALY combines survival and the quality of life into one measure. An important advantage of using QALY's as outcome of CEA, is that this makes it possible to compare interventions for different kind of health problems with different kind of health outcomes. In CBA, both costs and effects are valued in monetary terms. CBA is in theory a powerful technique since it can directly answer questions of allocative efficiency; however it is difficult to assign monetary value to health outcomes of an intervention. Finally, CMA seeks the least costly intervention (Brazier et al., 2007; Drummond et al., 2005). Of these four techniques, the CEA and CUA are the most commonly applied methods (Cunningham, 2001).

Regardless the type of economic evaluation, there are a couple of key aspects that are important to guarantee the validity of any economic evaluation. To start with, there should be a well defined question that clearly identifies the alternatives being compared and clarifies the viewpoint from which the comparison is made. Different viewpoints are possible; the most commonly used are the societal perspective and the heath care perspective. The viewpoint determines what costs and effects are taken in to account. Generally the societal perspectives is recommended since it takes into account all relevant costs and health benefits regardless of who experiences them. For preventive interventions it is recommended to use both the societal and the health care perspective (Van Baal et al., 2009; Drummond et al., 2005; Hunink et al., 2001).

In addition to the viewpoint chosen, it is important that a clear description of alternatives is given and all relevant costs and consequences for each alternative are identified and measured in appropriate physical units. In this, the time horizon chosen is important. The time horizon is the period of time covered by the analysis. This should be sufficiently long to reflect all important differences between the alternatives in terms of costs and effects. Often a lifetime horizon is preferred (Briggs et al., 2006; Drummond et al., 2005).

Furthermore, some indication of validation of effectiveness should be given. Evidence of effectiveness in economic evaluations often comes from different sources. In addition to the effectiveness evidence, economic evaluations require evidence related to resource use, unit costs and for CUA data on health related quality of life. A method to structure all this evidence from different sources is by using decision analytic models. Models give a simplified representation of reality and provide a framework for decision-making under uncertainty (Briggs et al., 2006; Drummond et al., 2005; Uyl-de Groot & Rutten-van Mölken, 2010).

Different types of models exist of which decision trees and markov models are most commonly applied. Common to all models is that they are based on some key elements i.e. probabilities and expected values. Probabilities represent the likelihood of events to occur. Expected values are expected costs and effects for each of the strategies that are compared (Briggs et al., 2006; Drummond et al., 2005).

## *Economic Evaluation of Public Health and Preventive Interventions*

Most economic evaluations focus on 'clinical' interventions such as drugs, devices and medical technologies. However, there is also increasing interest in economic evaluations for public health and preventive interventions since these also consume health care resources and money spent on public health and preventive interventions cannot be spent on other health care interventions (Drummond et al., 2007; Trueman & Anokye, 2013; Van Gils et al., 2011). Public health and preventive interventions aim to improve quality of life through promotion of healthy behaviors and environment (Simeons, 2011).

The methods for economic evaluations of clinical interventions are well developed. In contrast, the evaluation of public health interventions often raises additional methodological challenges. There are four main areas of methodological challenges in economic evaluations of public health interventions. First, the attribution of outcomes to interventions is in public health interventions often difficult since these interventions often have a broad range of consequences and the causal chain of effects is complex. Therefore, it is harder to obtain unbiased estimates of effects (Drummond et al., 2007; Victoria et al., 2004). An example of a public health intervention related to pregnancy is the mass media campaign for the periconceptional use of folic acid. It is advised to use folic acid from four weeks before conception until eight weeks thereafter in order to reduce adverse pregnancy outcomes, specifically neural tube defects (De Walle et al., 2002). To obtain the beneficial biological effects of folic acid, there are some behavioral steps required. For instance, the message should arrive at reproductive women and the women should comply with the recommendations and therefore planning pregnancy is required. To demonstrate whether the intervention is effective and caused a reduction in the prevalence of neural tube defects, the underlying steps need to be measured and understood (Victoria et al., 2004). At this moment, it is recommended to use clinical trials as source of evidence of effectiveness. However, when RCT's are not available, natural experiments and non-experimental data can be used (Drummond et al., 2007; Victoria et al., 2004). Second, it is not clear which methodology of economic evaluation is the most appropriate for public health interventions. However, the NICE (National Institute of Health Care Excellence) currently advises CUA. Third, standard economic evaluations often focus primary on efficiency consideration. However, in public health interventions equity considerations are of particular importance as well. For instance, public health programs often aim to reduce health inequalities. More research is needed to determine how to incorporating equity considerations in economic evaluations of public health interventions. Fourth, costs and consequences often occur intersectoral. It is recommended to quantify these costs and effects for each sector (Drummond et al., 2007).

Despite these methodological challenges, there is a need to conduct economic evaluations of public health and preventive interventions as economic evidence of good quality on these interventions is still scarce (Kelly et al., 2005; Swappach et al., 2007). In addition, a large amount of the disease burden in Western countries is caused by lifestyle related diseases that can be prevented. Therefore, prevention might be a better investment than cure. Still, only a minor part of the health care budget is spent on prevention in the Netherlands (Polder & Mackenbach, 2007). More evidence on effectiveness and cost-effectiveness might change this.

## Methods

To inform decision making in health care, modeling is a widely used technique. Models help to structure clinical and economical evidence by combining currently available evidence on health consequences and costs from different sources. Purpose of modeling is to estimate the effects of an intervention on health outcomes and costs (Weinstein et al., 2003). Different types of models can be used in economic evaluations. One of the simplest forms of a decision model is the decision tree. In the decision tree, the problem is the starting point of the model. Probabilities represent the likelihood of an event to occur. Several subsequent probabilities can be combined in the decision tree. To obtain the chance of a sequence of events, probabilities can be multiplied (Briggs et al., 2006; Hunink et al., 2001).

In this study, 'Slimmer Zwanger' is evaluated. Although the intervention is developed to change the unhealthy lifestyle behaviors of couples, it was chosen to evaluate 'Slimmer Zwanger' for women as the intervention is primarily offered to women. The subfertile population was chosen as this target group is easier to reach than the general population because they are expected to seek help and advice in fertility clinics.

A model was designed to compare the costs and effects of 'Slimmer Zwanger' to 'do nothing'. This comparator was chosen since no intervention such as 'Slimmer Zwanger' is available yet. However, as mentioned earlier other types of preconception care are available (Health Council of the Netherlands, 2007). For example, the department of Obstetrics and Gynaecology of the Erasmus University Medical Centre had an outpatient clinic on preconeptional counseling tailored on dietary intake and lifestyle. This is counseling is aimed at detecting and reducing unhealthy lifestyle behaviors of couples who are trying to become pregnant (Hammiche et al., 2011). Since this type of organized preconceptional counseling is still scares in the Netherlands (Health Council of the Netherlands, 2007) and Dutch guidelines for pharmaco-economic research recommend using the standard treatment (used in daily practice) as comparator in economic evaluations (Health Insurance Council, 1999). For this study, 'Do nothing' was chosen as the comparator.

In this study, it was chosen to evaluate the cost-effectiveness of 'Slimmer Zwanger' from both the societal and heath care perspective and with a time horizon of one year. The health care perspective was chosen, since most relevant costs and effects in short term, seem to lie within the health care system. This was complemented with the societal perspective as this is generally considered to be the preferred perspective in health care decision making regarding preventive interventions. Particularly in lifestyle interventions, which are developed to let individuals live a longer and healthier life (Baal et al., 2009; Hunink et al., 2001). In addition, Van Baal et al. (2009) recommend evaluating preventive interventions both from the societal perspective and the health care perspective.

A relatively short time horizon of one year was chosen since this is the first modeling study which evaluates the cost-effectiveness of 'Slimmer Zwanger'. A short term evaluation should give a first indication of cost-effectiveness of this new intervention.

### *Population*

The population studied is the subfertile population in the Netherlands, aged 18-45 who seek help and advice in fertility clinics. This is about 13% of the reproductive population. In the Netherlands approximately 250000 couples are trying to become pregnant. This implies that approximately 32500 couples are affected by subfertility (R.P.M. Steegers-Theunissen, personal communication).

### *Model Structure*

For the three research questions, three decision trees were structured represented in figure 1, 2 and 3. The square in the decision tree indicates a decision point between alternative options and the circles indicate points where different alternative events are possible (Briggs et al., 2006). The three models have different outcomes, reflecting a range from intermediate to final outcomes. The main outcome of model 1 is a reduction in unhealthy lifestyle behaviors, either in percentage of women achieving a complete healthy lifestyle, or a reduction in number of unhealthy lifestyle behaviors. Main outcome of model 2 is percentage pregnancies achieved. The percentage healthy babies born is the outcome of model 3. Each outcome relates to a research question. The trees are represented separately however, model 2 is subsequent to model 1 and model 3 is subsequent to model 2.

To construct the decision trees, a rational approach to health care decision making, described by Hunink et al. (2001) was used. The structure of the model is mainly based on the review of Bonsel et al. (2010), Homan et al. (2007) and other literature. We aimed to use the best evidence available at the moment the model was built. The literature used, describes the association between the variables used in the model. After the decision problem was defined and subsequent models were structured, it was tested if the mathematical calculations were accurate. This was done by using extreme input values to test whether they produce the expected outcomes. After this, the models were validated by an expert (R.P.M. Steegers-Theunissen, personal communication).

Model 1 starts with theoretically subfertile women who have a child wish and who seek help and advice in fertility clinics. They can either use 'Slimmer Zwanger' or 'do nothing'. This will result in having a healthy lifestyle or in having several unhealthy lifestyle behaviors. The following unhealthy lifestyles behaviors were used; unhealthy BMI, smoking, not using folic acid, unhealthy nutrition and lack of physical activity. Insufficient vegetables or fruit was used as a proxy for unhealthy nutrition. Although other unhealthy lifestyle behaviors exist, from the literature is known that these influence the probability for women to become pregnant.

Women with just one unhealthy lifestyle behavior are split up into the specific lifestyle behaviors i.e. unhealthy BMI, smoking, not using folic acid, insufficient vegetables/fruit and lack of physical activity. When women have two to four unhealthy lifestyle behaviors, this can be a mixture of unhealthy BMI, smoking, not using folic acid, insufficient vegetables/fruit and lack of physical activity. However, the prevalence of specific combinations of these lifestyle behaviors is unknown. When women have five unhealthy lifestyle behaviors, they will have all the five unhealthy behaviors that are considered in the models.

It was chosen to represent the unhealthy lifestyle behaviors cumulative in the models and not separately, since research has shown that approximately 6% of the couples who are trying to become pregnant have a completely healthy lifestyle, about 30% of couples have only one unhealthy lifestyle behavior, 36.1% have two, 18.1% have three and 8.2% have four or more unhealthy lifestyle behaviors. This implies that over 60% of couples who are trying to become pregnant have more than one unhealthy lifestyle behavior (Hassan & Killick, 2004). These results were found in the US population, however Dutch research about the lifestyle behaviors of the general Dutch population show similar results, with approximately 10% of the population with a completely healthy lifestyle, 32% with one, 37% with two and 20% with three or four unhealthy lifestyle behaviors (Schuit et al., 2002). The frequency of unhealthy lifestyle behaviors of the subfertile population is comparable to the frequency in the general population (Hammiche et al., 2011).

Model 2 is an addition to model 1. When subfertile women have a healthy lifestyle or one to five unhealthy lifestyle behaviors, they can either become pregnant or not. For women who do not become pregnant, it was assumed they start fertility treatment, however what happens after this is beyond the scope of the current modeling approach.

Model 3 is an addition to model 2. Women who become pregnant can either have a healthy baby or a BIG3 (preterm birth, low birth weight and birth defects) baby. Although there is a fourth important risk factor associated with perinatal mortality, from the literature it is known that the BIG3 disorders are influenced by lifestyle behaviors.

For all models a time horizon of one year was chosen. However, pregnancy usually takes nine months and therefore, some of the women who become pregnant within one year, will have birth after one year. Theoretically these babies will fall outside the time horizon of the models. Therefore, it was assumed that all women who become pregnant within one year will give birth within one year. This limitation is a characteristic of decision tree modeling since time is not explicitly defined in a decision tree. When a fixed time horizon is used, events cannot occur at different points in time (Drummond et al., 2005; Hunink et al., 2001).

**Figure 1.** *Decision Tree model 1*

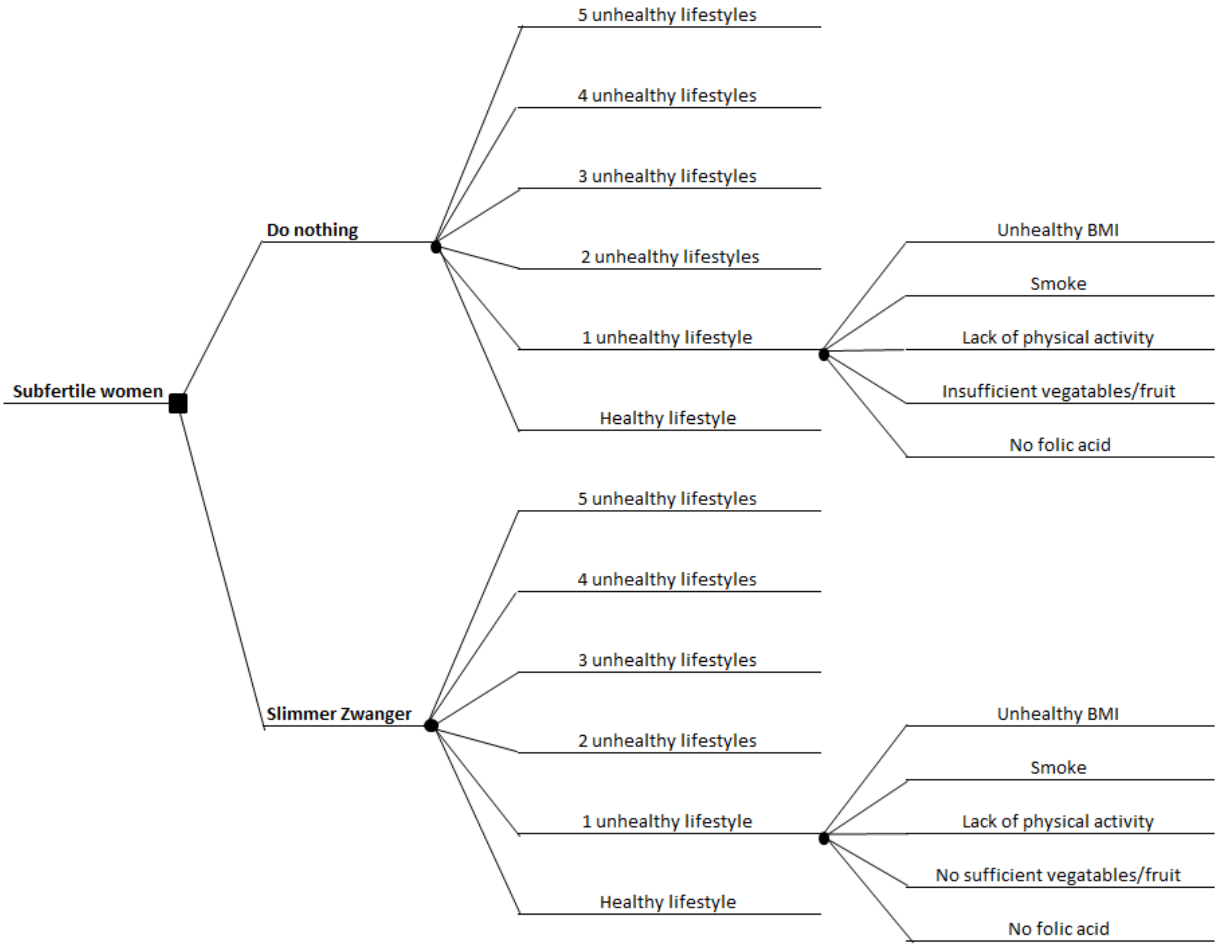


**Figure 2.** *Decision Tree model 2*

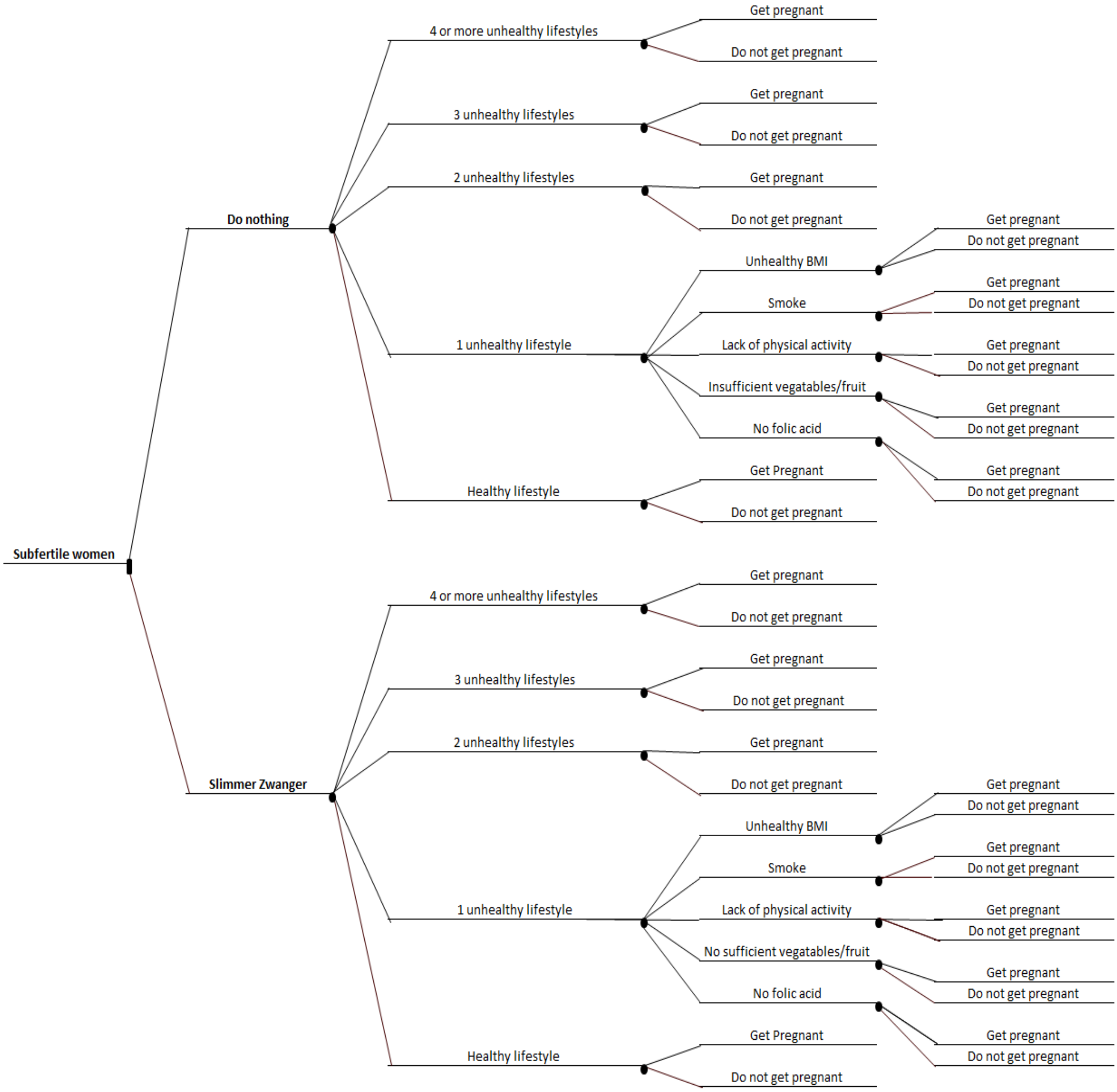
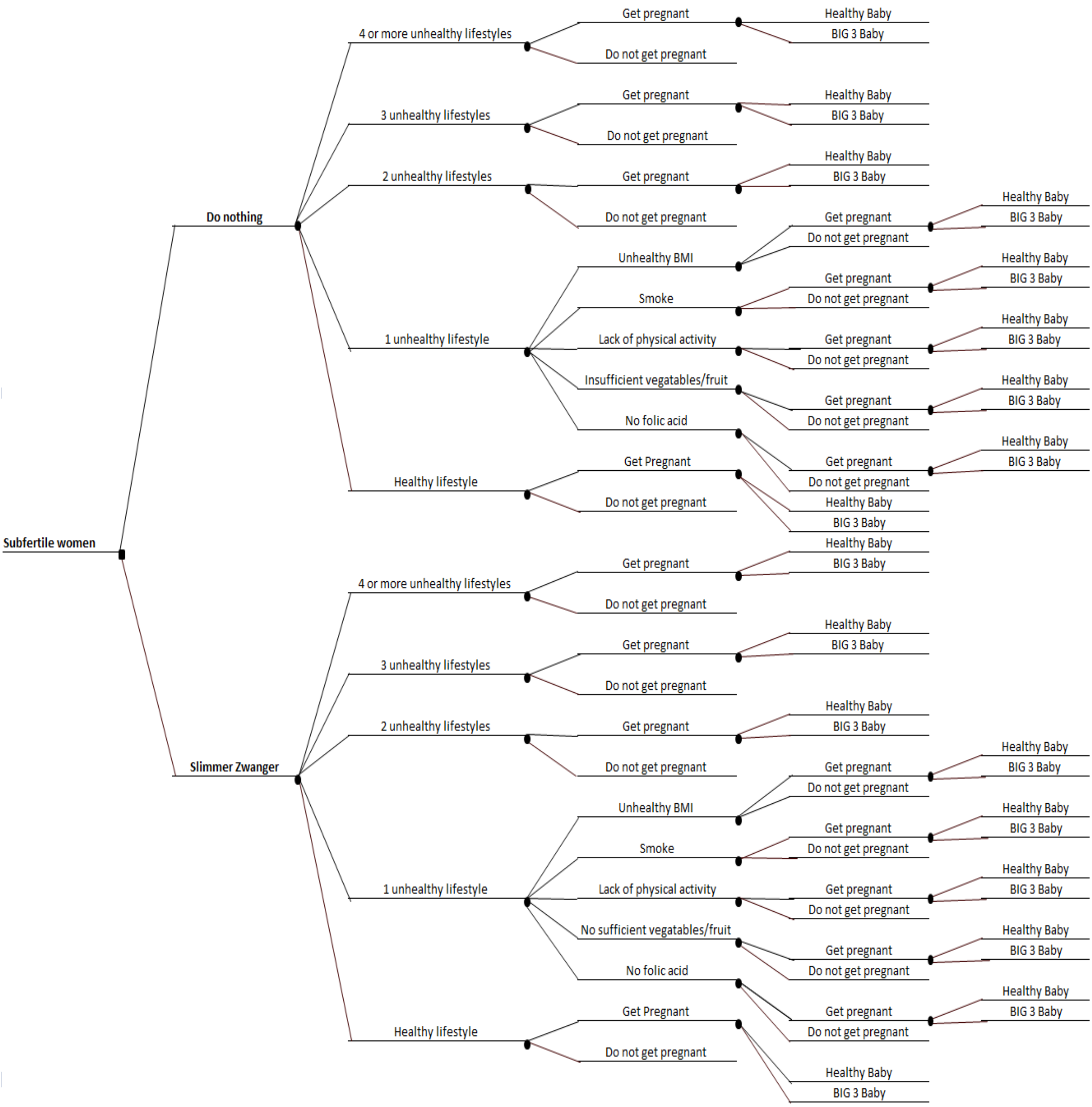


**Figure 3**. *Decision tree model 3*



## *Model Inputs*

### *Probabilities*

The probability data that were used as input data for the three different decision trees were derived from different sources.

#### *Probabilities Model 1*

For model one, the probabilities were derived from the survey data from the Erasmus MC. The data included information on several lifestyle and nutritional behaviors of couples who are trying to become pregnant and how these change over time while using 'Slimmer Zwanger'. Measurements were done prior to the use of 'Slimmer Zwanger'and after 6, 12, 18 and 24 weeks. The women surveyed were both subfertile and fertile women. Since the population of interest for this study is the subfertile population, it was assumed that the lifestyle behaviors of subfertile women are comparable to the lifestyle behaviors of the surveyed women. This is in line with previous research which showed that the prevalence of unhealthy lifestyle behaviors is similar in the subfertile and in the general population (Hammiche et al., 2011).

The survey data contained information about the following lifestyle behaviors; folic acid use, BMI, smoking behavior, several categories of nutritional habits and physical activity. No information about alcohol consumption of the women was available and therefore this lifestyle behavior was not included in the model. The first measure (at 0 weeks) was prior to the use of the 'Slimmer Zwanger' program. Therefore, this measure was used to derive the probabilities of having zero to five unhealthy lifestyle behaviors of the 'do nothing' option. The second measure (after 6 weeks) was used to derive the probabilities of having zero to five unhealthy lifestyles of the 'Slimmer Zwanger' option. This measure at week six was used since the measures after week six contained fewer observations.

The first measure contained information on the variables of interest of 601 individuals (521 females and 80 males). However, there was only information available of 25 women at the second measure on all the variables of interest (week 6). This was primarily caused by missing data of smoking behavior, however these data were missing since the question about smoking was not asked again at the women who did not smoke. Therefore, the data of smoking behavior of those who did not smoke at t=0, were carried forward to week six. This resulted in 227 observations at week six of all the variables of interest. These 227 observations were used to derive probabilities for the number of unhealthy lifestyle behaviors.

To derive the probabilities of the cumulative lifestyles behaviors, the five lifestyle behaviors were coded one when 'unhealthy' and zero when 'healthy'. A new variable was created in which the lifestyle behaviors were added. The lifestyle behaviors were categorized as 'unhealthy' when recommendations were not met. Implying, not using folic acid, being underweight/overweight/severely overweight, insufficient consumption of vegetable and/or fruit, being physically active for less than 28 minutes a day and smoking.

Probabilities of subfertile women of having zero to five unhealthy lifestyle behaviors and probabilities of having zero to five unhealthy lifestyle behaviors of women who use 'Slimmer Zwanger' are displayed in table 1.

**Table 1.** *Probabilities model 1*

| | Frequency | Probability (%) | α[1] | β[2] | Source |
|---|---|---|---|---|---|
| **Nr. of unhealthy lifestyle behaviors in subfertile population at intake (N=227)** | | | | | Survey data t=0 |
| **0** | 3 | 1.3 | 3 | 224 | |
| 1 | 16 | 7.0 | 23 | 204 | |
| 2 | 107 | 47.1 | 75 | 152 | |
| 3 | 75 | 33.0 | 107 | 120 | |
| 4 | 23 | 10.1 | 16 | 211 | |
| 5 | 3 | 1.3 | 3 | 224 | |
| Total | 227 | 100 | | | |
| **Nr. of unhealthy lifestyles behaviors of subfertile population after 6 weeks of using 'Slimmer Zwanger'(N=227)** | | | | | Survey data t=6 |
| **0** | 10 | 4.4 | 10 | 217 | |
| 1 | 42 | 18.5 | 42 | 185 | |
| 2 | 105 | 46.3 | 105 | 122 | |
| 3 | 55 | 24.2 | 55 | 172 | |
| 4 | 13 | 5.7 | 13 | 214 | |
| 5 | 2 | 0.9 | 2 | 225 | |
| Total | 227 | 100 | | | |

[1] Number of events of interest observed from the sample.
[2] Sample size minus number of events of interest

### *Probabilities Model 2*

Both the literature, expert opinion and the survey data from the Erasmus MC were used to derive the probabilities of model 2.

First, no literature was available about the probability to become pregnant within one year with a completely healthy lifestyle. Therefore, the assumption was made that (50% * 1.3 =) 65% of subfertile couples with a completely healthy lifestyle will have a spontaneous pregnancy within twelve months. This assumption was based on the opinion of an expert, who predicted that without taking into account lifestyle, 50% of the subfertile population will become pregnant spontaneously within one year (R.P.M. Steegers-Theunissen, personal communication). This combined with an expected relative risk reduction of 30% for women who have a completely healthy lifestyle. This assumed probability of 0.65, was used to calculate the probabilities to become pregnant with one to five unhealthy lifestyle behaviors. Relative Risks (RR) and Odds Ratios (OR) of pregnancy with several unhealthy lifestyle behaviors and with the specific unhealthy lifestyle behaviors were obtained from the literature and multiplied by the probability to become pregnant with a completely healthy lifestyle (0.65). Although Relative Risks are different from Odds Ratios, RRs and ORs are used interchangeably as for small probabilities the Relative Risk is approximately equal to the Odds Ratio (Kirkwood & Sterne, 2011).

Second, to determine the probability to become pregnant with one unhealthy lifestyle behavior, the probabilities of having the specific unhealthy lifestyle behaviors (unhealthy BMI, smoking, not using folic acid, insufficient vegatables/fruit and lack of physical activity) for the subfertile and 'Slimmer Zwanger' population were calculated using the survey data (t=0 and t=6). Results show that more women in the 'Slimmer Zwanger' population have one unhealthy lifestyle behavior than in the 'do nothing' population. In addition, there is a different distribution of the specific lifestyle behaviors within one unhealthy lifestyle behavior in the 'Slimmer Zwanger' and 'do nothing' population. Implying 'Slimmer Zwanger' reduces the number of unhealthy lifestyle behaviors and in addition changes the types of unhealthy behaviors.

Odds Ratios of the specific lifestyle behaviors obtained from the literature were multiplied by 0.65. The ORs of BMI and smoking could be used directly from the literature since these were the ORs of ongoing pregnancy with an unhealthy compared to a healthy BMI and for smokers compared to non-smokers. Rich-Edwards et al. (2002) suggest there is no evidence that moderate physical activity affects fertility, therefore an OR of 1 was used for physical activity. However, the ORs of folic acid and nutrition had to be converted. The nutrition OR obtained from the literature was based on a preconception diet score, that ranged from zero to six, where six represented a highly adequate nutrition. Twigt et al. (2012) suggested that an additional point on the PDR-score is associated with an increased chance of ongoing pregnancy of 65% (OR 1.65). This implies, 1.65 lower chance of ongoing pregnancy with one point lower on the PDR score, and therefore an OR of 0.606 (1/1.65 = 0.606 OR). Chavarro et al. (2008) reported an OR of 0.41 of subfertility for women who had high intake of folic acid compared to no intake. For our study, the risk of interest was the risk of ongoing pregnancy for women with no folic intake compared to women who do take folic acid supplements. It was assumed that this was 0.41, based on Chavarro et al. (2008). The distribution of the specific lifestyles and the probabilities, ORs are represented in table 2.

To calculate the pregnancy probabilities for two to five unhealthy lifestyle behaviors the paper by Hassan & Killick (2004) was used. They describe the relative risks of couples of having a time to pregnancy (TTP) longer than one year when having one to four (or more) unhealthy lifestyle behaviors, compared to couples with a completely healthy lifestyle. For model 2, RRs to become pregnant within one year were needed. These were calculated with the findings of Hassan & Killick (2004) (table 3) and used to estimate the probabilities to become pregnant within in one year (table 2).

The specific lifestyle behaviors Hassan & Killick (2004) included in the cumulative lifestyles were; women's smoking > 15 cigarette's each day, men's smoking > 15 cigarette's each day, men's alcohol consumption > 20 units each week, women's coffee and tea consumption ≥ 7 cups each day, women's weight > 70 kg, social deprivation score > 60, women's age > 35 years, and/or partner age > 45 years at time of conception. These lifestyle behaviors differed from the lifestyle behaviors included in model 1 of our study. In addition, the population studied by Hassan & Killick (2004) was the general population while the population of interest for model 1, 2 & 3 was the subfertile population. However, for this moment this was the best evidence available. Therefore, it was assumed that relative risks of TTP more than one year, with lifestyle behaviors used in our study for the subfertile population, were comparable to the relative risks described by Hassan & Killick (2004).

Since Hassan & Killick (2004) describe the risk of subfertility of zero to four or more unhealthy lifestyle behaviors and not of five unhealthy lifestyle behaviors. Four or more unhealthy lifestyle behaviors were used for model 2 and 3 by adding the probabilities of four and five unhealthy lifestyle behaviors.

**Table 2.** *Probabilities model 2*

| | Frequency | Probability (%) | Relative Risk | α | β | Source |
|---|---|---|---|---|---|---|
| **One unhealthy lifestyle behavior in the subfertile population at intake** | | | | | | Survey data t=0 |
| BMI | 2 | 13 | | 2 | 14 | |
| Smoking | 1 | 6 | | 1 | 15 | |
| Physical activity | 8 | 50 | | 8 | 8 | |
| Vegetables/fruit | 5 | 31 | | 5 | 11 | |
| Folic acid | 0 | 0 | | 0 | 16 | |
| Total | 16 | | | | | |
| **One unhealthy lifestyle behavior in the subfertile population after 6 weeks** | | | | | | Survey data t=6 |
| BMI | 8 | 19 | | 8 | 34 | |
| Smoking | 1 | 2 | | 1 | 41 | |
| Physical activity | 27 | 64 | | 27 | 15 | |
| Vegetables/fruit | 6 | 14 | | 6 | 36 | |
| Folic acid | 0 | 0 | | 0 | 42 | |
| Total | 42 | | | | | |
| **Pregnancy with unhealthy lifestyle behavior** | | | | | | |
| BMI | | 44 | 0.67 OR | 44 | 56 | Lintsen et al (2005) |
| Smoking | | 43 | 0.66 OR | 43 | 57 | Augood et al. (1998) |
| Physical activity | | 65 | 1 OR | 65 | 35 | Rich-Edwards et al. (2002) |

| | | | | | |
|---|---|---|---|---|---|
| Vegetables/fruit | 39 | 0.61 OR | 39 | 61 | Twigt et al. (2012) |
| Folic acid | 27 | 0.41 OR | 27 | 73 | Chavarro et al. (2008) |
| **Pregnancy with:** | | | | | |
| Healthy lifestyle | 65 | 1 | 65 | 35 | Steegers-Theunissen, personal communication |
| Two unhealthy lifestyles | 48 | 0.74 | 48 | 52 | Hassan & Killick (2004) |
| Three unhealthy lifestyles | 40 | 0.62 | 40 | 60 | Hassan & Killick (2004) |
| Four or more unhealthy lifestyles | 30 | 0.46 | 30 | 70 | Hassan & Killick (2004) |

**Table 3.** *Calculation Relative Risks of pregnancy within one year*

| | **Prevalence lifestyles in population** | **Absolute nr of total N = 1976** | **conception rates within in 1 year** | **Nr. Of conceptions** | **Nr. no conception** | **Total nr.** | **Relative Risk** |
|---|---|---|---|---|---|---|---|
| **0 unhealthy lifestyle behaviors** | 5.7% | 112.6 | 83.3% | 93.8 | 18.8 | 112.6 | 1 |
| **1 unhealthy lifestyle behavior** | 31.9% | 630.3 | 71.4% | 450.1 | 180.3 | 630.3 | 0.86 |
| **2 unhealthy lifestyle behaviors** | 36.1% | 713.3 | 61.5% | 438.7 | 274.6 | 713.3 | 0.74 |
| **3 unhealthy lifestyle behaviors** | 18.1% | 357.7 | 51.7% | 184.9 | 172.7 | 357.7 | 0.62 |
| **>4 unhealthy lifestyle behaviors** | 8.2% | 162.03 | 38.4% | 62.2 | 99.81 | 162.03 | 0.46 |

### *Probabilities Model 3*

The probabilities to give birth to a healthy baby and the probabilities to have a baby with BIG3 disorders, given the number of unhealthy lifestyle behaviors, were needed as inputs for model 3. The literature was used to estimate these probabilities. A number of assumptions had to be made due to lack of information.

To our knowledge, no literature is available which describes the probability of having a healthy/BIG3 baby with the different numbers of unhealthy lifestyle behaviors. However, Bonsel et al. (2010) described that 13.6% of all the babies born in the Netherlands, are babies with a BIG3 disorders. Therefore, it was assumed that women from the general population have on average two unhealthy lifestyle behaviors. And thus, with two unhealthy lifestyle behaviors a probability of having a baby with a BIG3 disorder of 0.136. This probability was used to calculate the probabilities of having a BIG3 baby with zero, three and four (or more) unhealthy lifestyle behaviors by using an OR of 1.3 (probability * 1.3). This resulted in a probability of 0.176 (0.136 * 1.3), 0.229 (0.176*1.3), 0.08 (0.136/1.3^2) for three, four and zero unhealthy lifestyle behaviors respectively. The 1.3 OR was based on the opinion of an expert since no literature about this was available (R.P.M. Steegers-Theunissen, personal communication).

For one unhealthy lifestyle behavior, the distribution of the specific unhealthy lifestyle behaviors (unhealthy BMI, smoking, not using folic acid, insufficient vegetables/fruit and lack of physical activity) (table 2) was used to determine the probability of having a BIG3 baby with one unhealthy lifestyle behavior. Risks (RR/OR) of BIG3 with the specific lifestyle behaviors obtained from the literature were multiplied by 0.08 (probability of BIG3 with 0 unhealthy lifestyle behaviors), this resulted in probabilities of 0.09; 0.16; 0.02; 0.10; and 0.08 for unhealthy BMI, smoking, not using folic acid, insufficient vegetables/fruit and lack of physical activity respectively (table 4).

The literature used, described the RRs or ORs of the specific lifestyles compared to not having these lifestyles (unhealthy BMI, smoking, not using folic acid, insufficient vegetables/fruit and lack of physical activity) on the separate BIG3 outcomes i.e. pre-term birth, low birth weight and birth defects. The prevalence of these outcomes in the Dutch population is 5.5%, 6.3% and 1.8% respectively when only singular diagnoses are considered (Bonsel et al., 2010). Hence, of BIG3 the distribution is 40.4% pre-term birth, 46.4% low birth weight and 13.3% birth defects. This distribution was used to weigh the risks obtained from the literature (represented in table 4) and estimate the risks of BIG3 as combined outcome. Combination diagnosis were not taken into account, since adding the probabilities of combination diagnosis to the singular diagnosis probabilities would result in double counting and overestimate the prevalence of BIG3.

Some Relative Risks or Odds Ratio's described in the literature needed some adjustment to fit to the selected population and variables:

- BMI. Djelantik et al. (2012) described the contribution of overweight (BMI 25-30) and obesity (BMI > 30) on low birth weight and pre-term birth. The prevalence of overweight was 17.3% and of obesity 6.3%. Relative risks of low birth weight were 0.99 and 1.09 for overweight and obesity respectively compared to normal BMI (18.5 -25). The RRs of obesity and overweight were combined to create a category of unhealthy BMI (distribution of overweight and obesity is 73.3% and 26.7%) 0.733*0.99 + 0.267*1.09= 1.02 RR. The same was done for pre-term birth, with a RR of 1.17 and 1.63 for overweight and obesity respectively (1.17*0.733 + 1.63*0.267 = 1.29 RR).
- Smoking. Hackshaw et al. (2011) expected an OR of 1.05-1.10 of smoking compared to non-smoking when all birth defects are combined. For our model, we the average OR of 1.075 was used as the exact OR is unknown.
- Folic acid. Botto et al. (2004) suggested that using folic acid in the periconceptional period reduces the risk of birth defects with an OR between 0.53-0.80 when all birth defects are combined. Since for our study, the risk of interest is the risk of birth defects when no folic acid is used, the ORs were converted. The risk of birth defects is expected to lie between

1.25-1.89 OR (1/0.53= 1.89 and 1/0.80=1.25) when no folic is used. No exact number is known and therefore, the average 1.57 was used in our model (1.25 + 1.89/2=1.57).

- Vegetables/fruit. To our knowledge no literature is available that describes the effects of insufficient vegetables/fruit on BIG 3. Therefore, a relative risk of 1.3 of BIG3 of insufficient compared to sufficient vegetables/fruit was assumed, based on the opinion of an expert (R.P.M. Steegers-Theunissen, personal communication).

- Physical activity. Chasan-Tabar et al. (2008) reviewed the association between recreational physical activity and birth weight. The majority of studies observed a neutral or protective effect. However, the assessments methods of recreational physical activity were often limited. Therefore, it was assumed that RR of recreational physical activity on low birth weight was 1.

- Physical activity. Leiferman et al. (2003) suggested that there is no association between regular physical activity and pre-term birth. In addition, literature which describes the association between birth defects and physical activity was lacking, and therefore this was assumed to be 1.

In table 4 all probabilities and corresponding literature sources are represented.

**Table 4.** *Probabilities model 3*

| | Distribution BIG3 (%) | Probability BIG3(%) | Relative Risk | A | β | Source |
|---|---|---|---|---|---|---|
| **Unhealthy BMI** | | | | | | |
| **Pre term birth** | 40.4 | | 1.29 RR | | | Djelantink et al. (2012) |
| **Low Birth weight** | 46.4 | | 1.02 RR | | | Djelantink et al. (2012) |
| **Birth defects** | 13.2 | | 1.3 OR | | | Blomberg et al. (2009) |
| **Combined BIG3** | 100 | 9.4 | 1.17 | 9 | 91 | |
| **Smoking** | | | | | | |
| **Pre term birth** | 40.4 | | 2.15 RR | | | Djelantink et al (2012) |
| **Low Birth** | 46.4 | | 2.14 RR | | | Djelantink |

| | | | | | | |
|---|---|---|---|---|---|---|
| | **weight** | | | | | et al (2012) |
| | **Birth defects** | 13.2 | | 1.075 OR | | | Hackshaw et al. (2011) |
| | **Combined BIG3** | 100 | 16 | 2.00 | 16 | 84 | |
| **No Folic Acid** | | | | | | | |
| | **Pre term birth** | 40.4 | | 1.01 RR | | | Lassi et al. (2013) |
| | **Low Birth weight** | 46.4 | | 1.00 | | | Shah et al. (2009) |
| | **Birth defects** | 13.2 | | 1.57 OR | | | Botto et al. (2004) |
| | **Combined BIG3** | 100 | 8.1 | 1.01 | 8 | 92 | |
| **Insufficient vegetables/fruit** | | | | | | | |
| | **Combined BIG3** | | 10.4 | 1.3 | 10 | 90 | |
| **Lack of physical activity** | | | | | | | |
| | **Pre term birth** | 40.4 | | 1.00 OR | | | Leiferman, et al. (2003) |
| | **Low Birth weight** | 46.4 | | 1.00 OR | | | Chasan-Tabar et al. (2008) |
| | **Birth defects** | 13.2 | | 1.00 | | | |
| | **Combined BIG3** | 100 | 8.3 | 1.03 | 8 | 92 | |
| **Healthy lifestyle** | | | 8.0 | | 8 | 92 | |
| **2 unhealthy** | | | 13.6 | | 14 | 86 | |

| | | | |
|---|---|---|---|
| **lifestyles** | | | |
| **3 unhealthy lifestyles** | 17.6 | 18 | 82 |
| **4 or more unhealthy lifestyles** | 22.9 | 23 | 77 |

### ***Costs***

Costs are calculated from both the societal perspective and the health care perspective. The perspective determines the costs and consequences that are included. When the societal perspective is used, all relevant costs and health benefits regardless of who experiences them are taken into account. When the health care perspective is taken, all health care costs and health benefits are considered (Hunink et al. 2001; Van Baal et al., 2009). Because of the brief time horizon of one year, down-stream costs are not taken into account. Below the costs are described for the three different models.

#### *Cost Model 1*

For the heath care perspective the only costs considered were the costs of 'Slimmer Zwanger'. The tariff for making use of this service is € 29.95 per half a year, including text messages, insurance, overhead and maintenance of 'Slimmer Zwanger'. This tariff is considered to be an indication for the actual costs.

For the societal perspective patient costs of having a healthy or several unhealthy lifestyle behaviors were considered as well. Costs of the specific lifestyle behaviors (smoking, folic acid use, healthy nutrition and physical activity) were obtained from the literature. These costs were combined to estimate the costs of having one unhealthy lifestyle behavior and the costs of having four unhealthy lifestyle behaviors. The distribution of the unhealthy lifestyle behaviors in those who have one unhealthy lifestyle behavior differed between 'Slimmer Zwanger' and 'do nothing', therefore the related costs differed as well. The costs of having two or three unhealthy lifestyle behaviors were estimated, assuming a positive linear relationship between the number of unhealthy lifestyle behaviors and the costs (starting with one unhealthy lifestyle up to four). All costs used in model 1 are represented in table 5.

**Table 5.** *Costs model 1*

| Perspective | Type of costs | Costs | Unit price (€) annually | α | β | Source |
|---|---|---|---|---|---|---|
| **Health care perspective** | Health care costs | Slimmer Zwanger | 59.90 | 1 | 59.9 | |
| **Societal perspective** | Patient costs unhealthy lifestyle | Healthy lifestyle | 564.80 | 1 | 564.8 | |
| | | 1 unhealthy lifestyle subfertile population | 452.72 | 1 | 452.72 | |
| | | 2 unhealthy lifestyles subfertile population | 850 | 1 | 850 | |
| | | 3 unhealthy lifestyles subfertile population | 1400 | 1 | 1400 | |
| | | 4 unhealthy lifestyles subfertile population | 1882.60 | 1 | 1882.60 | |
| | | 5 unhealthy lifestyles subfertile population | 1882.60 | 1 | 1882.60 | |
| | | 1 unhealthy lifestyle SZ population | 343.53 | 1 | 343.53 | |
| | | 2 unhealthy lifestyles SZ population | 810 | 1 | 810 | |
| | | 3 unhealthy lifestyles SZ population | 1400 | 1 | 1390 | |
| | | 4 unhealthy lifestyles SZ population | 1882.60 | 1 | 1882.60 | |
| | | 5 unhealthy lifestyles SZ population | 1882.60 | 1 | 1882.6 | |
| | Costs of cigarette smoking | | 1882.63[1] | | | |
| | Costs of healthy nutrition | | 113.15[2] | | | De Mul et al. |

| | | | |
|---|---|---|---|
| | | | (2009) |
| | Costs of physical activity | 388.80[3] | NIBUD, (2003) |
| | Costs of folic acid | 62.88[4] | De Weerd (2004) |

[1] An average women who smokes in the Netherlands, smokes 14 cigarettes a day (Stivoro, 2012). Annually this is 14*365= 5110 cigarettes. The price of one package of cigarettes costs approximately €7 and contains 19 cigarettes (http://www.prijsvansigaretten.nl). 5110/19 = 269 package of cigarettes each year * €7 is € 1882.63 annually.

[2] According to De Mul et al. (2009), the additional costs of a healthy nutrition compared to unhealthy nutrition are €0.31 daily. This implies 0.31 * 365= €113.15 costs annualy.

[3] It is estimated that in the Netherlands, the costs of exercising are on average € 32.4 each month (NIBUD, 2003).This implies € 32.4*12= € 388.8 annually

[4] Costs of folic acid use are 5.24 each month (De Weerd et al., 2003) * 12 so € 62.88 annually.

*Cost Model 2*

The health care costs for women who become pregnant were considered to be zero. The costs for women, who do not become pregnant, were considered to be those of assisted reproductive treatment (ART) (table 6). Costs of fertility treatment for both the health care and societal perspective were obtained from the paper by Fiddelers et al. (2009).

A widely used ART technique in the Netherlands is IVF. This type of treatment is only one of a series of assisted reproductive treatments used. However, IVF is the most commonly applied treatment (Andersen et al., 2007). Therefore, the costs of IVF were used in our model and it was assumed that costs of other reproductive treatments are comparable. Furthermore, the costs of one IVF cycle were used for our model. This is a quite conservative approach since a complete IVF treatment can consist of several cycles and there are additional costs associated with each cycle (maximum of three cycles is standard policy in most European countries)(Andersen et al., 2007). The pregnancy rate after one cycle is approximately 25%, depending on the strategy used (Malizia et al., 2009).

The health care costs of an IVF cycle are estimated by Fiddelers et al. (2009) to be €4170 (table 6). These estimates include costs of hormonal simulation phase, ovum pick-up costs, laboratory phase costs, embryo transfer costs, costs of hospital admission days and other costs. Other health care costs are considered to be those of GP visit Fiddelers et al. (2009). In addition, the societal costs of an IVF treatment cycle were estimated by Fiddelers et al. (2009). These costs include, productivity costs, leave of absence, loss of leisure time, out of pocket costs, informal care, absence of voluntary work or housekeeping and other and together €719. (table 6).

**Table 6.** *Costs model 2*

| Type of costs | Costs | Unit price (€) annually | | α | β | Source |
|---|---|---|---|---|---|---|
| **Health care costs** | Fertility treatment 1 cycle IVF | 4170 | IVF treatment cycle per couple, total health care costs | | | Fiddelers et al. (2009) |
| | | 11 | | | | Fiddelers et al. (2009) |
| **Total** | | 4181 | | 1 | 4181 | |
| **Non health care costs** | | 719 | Per cycle | 1 | 719 | Fiddelers et al. (2009) |

### *Costs Model 3*

Health care costs considered for model 3 are the costs related to neonatal morbidity and mortality obtained from the paper of Chung et al. (2001). Chung et al. (2001) represent neonatal hospital costs plus costs related to hospital stay for different neonatal outcomes i.e. none/mild morbidity, moderate morbidity, severe morbidity and death. The average of the costs of the neonatal outcomes; moderate morbidity, severe morbidity and death were calculated. This average was used in our model as estimate of costs related to BIG3 costs. The costs of none or mild morbidity were used as estimates of the costs of having a healthy baby. The costs were converted into euros since Chung et al. (2001) represented the costs in dollars. A conversion rate of 0.77 was used, based on the exchange rate of 06-2013.

It was assumed that the delivery costs of the mothers were the same for mothers of healthy baby and mothers of babies with BIG3 disorders and therefore not included in our model. No societal costs were considered as no accurate estimates of these costs were available.

**Table 7.** *Costs model 3*

| Type of costs | Costs (€) annually | | α | β | Source |
|---|---|---|---|---|---|
| **Health care costs** | | | | | |
| **No or mild morbidity** | 200.97 | Per healthy baby | 1 | 200.97 | Chung et al. (2001) |
| **Moderate/severe/death** | 44582.74 | Per BIG3 baby | 1 | 44582.74 | |

### ***Main Assumptions***

As in any modeling study, assumptions were made to construct the model. In table 8 the main assumptions made are summarized.

**Table 8.** *Main assumptions*

| | **Assumption** |
|---|---|
| **Probabilities model 1** | Prevalence of unhealthy lifestyle behaviors is similar in the general and subfertile population |
| **Probabilities model 2** | 65% Of subfertile couples with a completely healthy lifestyle will have a spontaneous pregnancy within twelve months |
| | Chance of spontaneous pregnancy decreases with the number of unhealthy lifestyle behaviors as described in Hassan & Killick (2004) |
| **Probabilities model 3** | The subfertile population has on average two unhealthy lifestyle behaviors and of those 13.6% will have a baby with BIG3 disorders |
| | With each additional number of unhealthy lifestyle behavior, the probability on BIG3 increases * 1.3 OR |
| **Costs model 1** | There is a positive linear relationship between the number of unhealthy lifestyles and patient costs |
| **Cost model 2** | Costs of fertility treatment are comparable to the costs of IVF |
| **Costs model 3** | Cost related to neonatal morbidity and mortality are comparable to the costs related to BIG3 disorders |
| **Sensitivity analysis** | When counts of events, sample sizes and standard errors were not available, the sample size was assumed to be 100. To fit distributions to data, α and β were estimate by multiplying the probability*100 (α ) and 100- α (β) |

### ***Model Outputs***

Outcome measures of the economic evaluation were the costs and effectiveness. Costs were expressed in monetary terms. Three different outcomes measures for effects were used for the three different models. In model 1, effects were expressed as a completely healthy lifestyle achieved. In addition, effects were expressed as a reduction per number of unhealthy lifestyle behaviors. This was done by using a 'healthy scale'. The scale ranged from zero to five, where five points represented the best score implying a completely healthy lifestyle and zero the worst score implying five unhealthy lifestyle behaviors. For model 2, effects were expressed as achieved pregnancies and for model 3 as healthy babies born.

For both the 'Slimmer Zwanger' and 'do nothing' option, costs and effects were calculated. Based on this, the incremental costs effectiveness ratios (ICERs) were calculated. These were expressed as additional costs related to the probability of a completely healthy lifestyle, additional costs per one unhealthy lifestyles reduction, costs per additional achieved pregnancy and costs per additional healthy baby born. ICERs were calculated for both a health care and a societal perspective.

### *Sensitivity Analysis*

To address the uncertainties involved in the input parameters used for the models and to describe what this means for uncertainty of the output parameters of the models, a probabilistic sensitivity analysis was performed. For this purpose, first the distributions were fitted for the different input parameters used in the three models. It is common to use different distribution for different input parameters since these parameters all have other constraints.

Probability data have the constraint that they can only take a value between zero and one and they must sum to one. For this reason a beta distribution is often used to fit binomial probability data (with two categories). However, when probability data are multinomial (having more than two categories), a multivariate generalization of the beta distribution, the Dirichlet distribution, is more appropriate to use (Briggs et al., 2006). The Dirichlet distribution provides probabilistic probabilities over multiple branches and satisfies the requirement that the probabilities sum up to one (Briggs et al., 2003).

Dirichlet distributions were used to fit the probabilities of the number of unhealthy lifestyle behaviors used in model 1. The probability data of both the 'do noting' and the 'Slimmer Zwanger' option were multinomial, since both contain six branches that together add up to one. Beta distributions were used to fit the probabilities of model 2 and model 3. These probability data were binomial since there is only two options, either become pregnant or do not become pregnant and either have a healthy baby or have baby with BIG3 disorder.

Both the beta and the Dirichlet distribution are characterized by two parameters, α and β. The α can be set as the number of events (r) of interest. The β can be set as the number of observations within the sample (n), minus the events of interest (Briggs et al., 2006). The probabilities of the number of unhealthy lifestyle behaviors and the probabilities of the specific lifestyles within one unhealthy lifestyle were obtained from the survey data. Therefore, the α and β of these probabilities were known and used to fit the distributions (table 1 & 2). On the other hand, the α and β of the probabilities of pregnancy and healthy babies born (model 2 & 3), were unknown since these were based on expert estimation and several literature sources. For this reason, it was assumed that the sample size was 100 and therefore the alpha was the probability*100 and beta 100-α (table 2).

Costs parameters are constrained as well, since these are non-negative and infinite. The gamma distribution is commonly used to represent uncertainty in costs parameters where the α and β can be estimated by $\alpha= \mu^2/s^2$ and $\beta=s^2/\mu^2$ (Briggs et al., 2006). All cost data for model 1, 2 and 3 were fitted using this gamma distribution. Since no standard errors of cost data were available, it was assumed that the standard errors were the same as the sample means as recommended by Briggs et al. (2006) (table 5,6,7).

For the probabilistic sensitivity analysis the model inputs were picked randomly from the specific distributions. This was repeated 1000 times using Excel. The mean incremental costs and effects were calculated as well as the mean of the ICERs. In addition, cost effectiveness planes and cost effectiveness acceptability (CEACs) curves were used to represent uncertainties graphically.

### *Cost Effectiveness Planes*

Output of a probabilistic sensitivity analysis gives the distribution of incremental costs, incremental effects and ICERs. These can be represented in a cost effectiveness (CE) plane which is often used to represent the differences in effectiveness (x axis) per patient and the differences in costs (y axis) of the treatment minus the control intervention. The CE plane has four quadrants which represent different scenarios i.e. the North East (NE) quadrant implies more costs but also more effects, the North West (NW) quadrant implies more costs and less effects, the South West (SW) quadrant implies less costs and less effects and the South East (SE) quadrant implies less costs and less effects. In which the new treatment is compared to the old treatment.

In cost-effectiveness studies it is common to find more effects but also more costs (NE quadrant). If this is the case, it has to be decided whether the additional health benefits are worth the costs. When more effects and less costs are found (SE quadrant), a new treatment dominates the old treatment and it is appropriate to implement the new treatment. When fewer effects and more costs are found (NW quadrant), it is better to keep the old treatment instead of introducing the new. Finally, when less costs but also fewer effects are found (SW quadrant), it has to be decided whether the reduction in costs is worth the reduction in effects (Briggs et al., 2006).

### *Cost Effectiveness Acceptability Curves*

To graphically represent the uncertainties surrounding cost-effectiveness of health care interventions, cost effectiveness acceptability curves (CEACs) are often used. The CEACs are determined on the basis of the probability that an intervention is cost-effective with different values of the threshold ranging from 0 to infinity (Briggs et al., 1998; Fenwick et al, 2004). We do not know at what value of the threshold ‘Slimmer Zwanger’ is cost effective on the different outcomes, therefore representing the probability that ‘Slimmer Zwanger’ is cost effective at different values of the threshold is a useful.

# Results

## *Model 1 Expected Unhealthy Lifestyle Behaviors*

The expected effects, expected costs, incremental effects, incremental costs and the incremental costs effectiveness ratios (ICERs) of model 1 are summarizes in table 9.

The first expected effect of model 1 is the expected probability to have a completely healthy lifestyle. The expected effects found were 0.013 for 'do nothing' and 0.044 for 'Slimmer Zwanger'. This implies that out of 1000 women, 13 women will have a completely healthy lifestyle when nothing is done, while 44 women will have a completely healthy lifestyle when 'Slimmer Zwanger' is used.

The second expected effect for model 1 is the expected points on the 'healthy scale'. This 'healthy scale' ranges from zero to five, where five points implies that a woman has a completely healthy lifestyle and zero points implies that a woman has all five unhealthy lifestyle behaviors. An expected score of 2.52 on the 'healthy scale' for 'do nothing' and an expected score of 2.89 for women who use 'Slimmer Zwanger' was found. This implies that women who use 'Slimmer Zwanger' have a healthier lifestyle.

The expected health care costs per women for 'do nothing' were €0 and for 'Slimmer Zwanger' €60. When the societal perspective is taken, patient costs related to the different numbers of unhealthy lifestyle behaviors were also included. The expected societal costs per women for 'Slimmer Zwanger' were € 1005, while €1118 for 'do nothing'.

The incremental costs and effects are the differences between costs and effects of 'Slimmer Zwanger' and 'do nothing'. Incremental costs of €-113 per women, from the societal perspective were expected. This implies lower costs, when 'Slimmer Zwanger' is used compared with 'do noting'. From the health care perspective, €60 additional costs were expected.

The ICERs are the additional costs per additional effect of 'Slimmer Zwanger' compared to 'do nothing'. The expected costs per women who achieve a completely healthy lifestyle were €1945 when the health care perspective is used. When the societal perspective is used €-3678 was expected which indicated dominancy as more effects and less costs are found. The ICERs were expected to be €164 and €-310 (indication dominancy) per additional point on the 'healthy scale', for the health care and societal perspective respectively. Implying €164 and €-310 (dominance) per women who achieves a reduction of one unhealthy lifestyle behavior.

**Table 9.** *Expected effects, expected costs and ICER*

| **Treatment** | **Perspective** | **Expected Effect (%)** | **Expected cost (€)** | **Incremental Effect** | **Incremental Cost** | **ICER (€/effect) per** |
|---|---|---|---|---|---|---|
| **Model 1 'Do nothing'** | Health care | 0.013 | 0 | | | |
| **Model 1** | Health care | 0.044 | 60 | 0.031 | 60 | 1945 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **'Slimmer Zwanger'** | | | | | | |
| **Model 1 'Do nothing'** | Societal | 0.01 | 1119 | | | |
| **Model 1 'Slimmer Zwanger'** | Societal | 0.04 | 1005 | 0.031 | -113 | -3678 (dominant) |
| **Model 1 'Do nothing' healthy scale** | Health care | 2.52 | 0 | | | |
| **Model 1 'Slimmer Zwanger' healthy scale** | Health care | 2.89 | 60 | 0.366 | 60 | 164 |
| **Model 1 'Do nothing' healthy scale** | Societal | 2.52 | 1119 | | | |
| **Model 1 'Slimmer Zwanger' healthy scale** | Societal | 2.89 | 1005 | 0.366 | -114 | -310 (dominant) |
| **Model 2 'Do nothing'** | Health care | 0.44 | 2343 | | | |
| **Model 2 'Slimmer Zwanger'** | Health care | 0.47 | 2263 | 0.033 | -80 | -2389 (dominant) |
| **Model 2 'Do nothing'** | Societal | 0.44 | 3864 | | | |
| **Model 2 'Slimmer Zwanger'** | Societal | 0.47 | 3527 | 0.033 | -337 | -10081 (dominant) |
| **Model 3 'Do Nothing'** | Health care | 0.37 | 5371 | | | |
| **Model 3 'Slimmer** | Health care | 0.40 | 5196 | 0.029 | -175 | -5967 (dominant) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Zwanger'** | | | | | | |
| **Model 3 'Do Nothing'** | Societal | 0.37 | 6892 | | | |
| **Model 3 'Slimmer Zwanger'** | Societal | 0.40 | 6485 | 0.029 | -407 | -13872 (dominant) |

### *Model 2 Expected Pregnancies*

The expected costs, effects and incremental costs effectiveness ratios (ICERs) of model 2 are represented in table 9.

The expected effect of model 2, is the percentage of pregnancies achieved. It was estimated that 47% of subfertile women will achieve pregnancy when 'Slimmer Zwanger' is used and 44% of subfertile women will achieve pregnancy when nothing is done.

The expected health care costs for women who use 'Slimmer Zwanger' were €2263 and for those who 'do nothing' €2234. This resulted in €-80 of incremental costs, which implies costs savings when 'Slimmer Zwanger' is used. From the societal perspective, the expected costs were €3864 and €3527 for 'do nothing' and 'Slimmer Zwanger' respectively. This again resulted in expected cost savings of €337.

The ICERs for model 2 are the additional costs per achieved pregnancy. Expected costs per pregnancy are €-2389 (dominant) from the health care perspective and €-10081 (dominant) from the societal perspective. This implies more effects and lower costs which can be explained by the fact that more women achieve pregnancy when 'Slimmer Zwanger' is used. From the health care perspective, only costs are related to females who do not become pregnant. Since more women become pregnant when 'Simmer Zwanger' is used, lower costs are expected. For the societal perspective even more costs savings are expected.

### *Model 3 Expected Healthy Babies*

The expected costs, effects and incremental costs effectiveness ratios (ICERs) of model 3 are represented in table 9.

Effects of model 3 are the expected percentage of healthy babies born. These were expected to be 37% when 'do nothing' and 40% when 'Slimmer Zwanger' is used. This implies that out of the 100 subfertile women of whom 44 achieve pregnancy, 37 are expected to have a healthy baby when 'do nothing'. When 'Slimmer Zwanger' is used, out of 100 subfertile women of whom 47 achieved pregnancy, 40 are expected to have a healthy baby.

The health care cost associated with the birth of a healthy baby were expected to be €5371 when nothing is done and €5196 when 'Slimmer Zwanger' is used, resulting in €-175 of incremental costs. When the societal perspective is used, the expected costs were €6892 and €6485 for 'do nothing' and 'Slimmer Zwanger' respectively, resulting in €-407 incremental costs.

The expected ICERs for model 3 were €-5967 (dominant) and €-13872 (dominant) from the health care and societal perspective respectively. These are the additional costs per healthy baby born. These numbers are negative which indicates dominancy as the incremental costs are expected to be negative as well.

### *Results Sensitivity Analysis*

The outcomes of the probabilistic sensitivity analysis with 1000 iterations are represented in CE planes (figure 4-7). Uncertainties concerning the cost effectiveness of 'Slimmer Zwanger' compared to 'do nothing', are graphically represented in CEACs. The mean costs, mean effects, mean incremental costs and effects and corresponding ICERs are represented in table 10.

#### *Model 1 Completely Healthy Lifestyle*

**Figure 4.** *CE plane model 1 with outcome 'Completely healthy lifestyle' when the health care perspective is used*

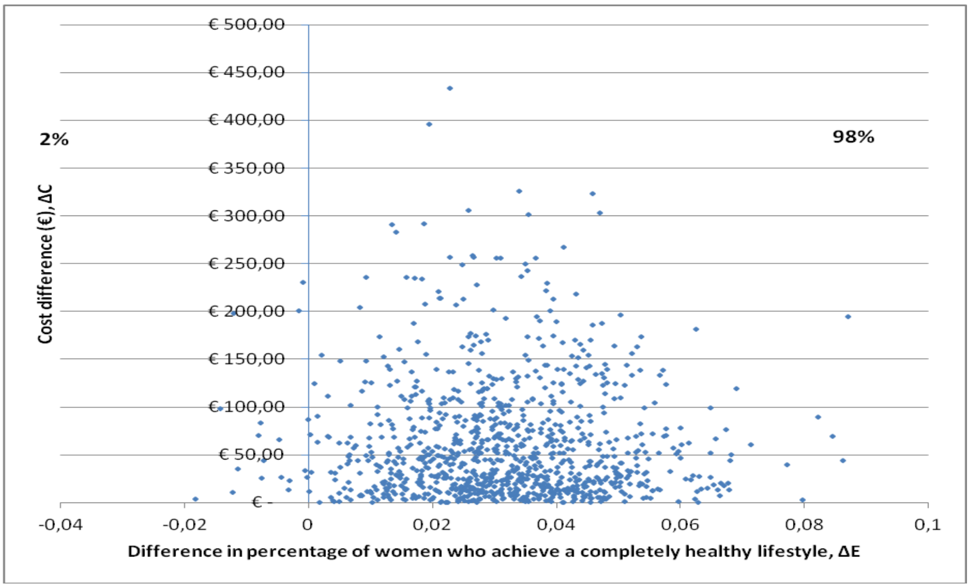
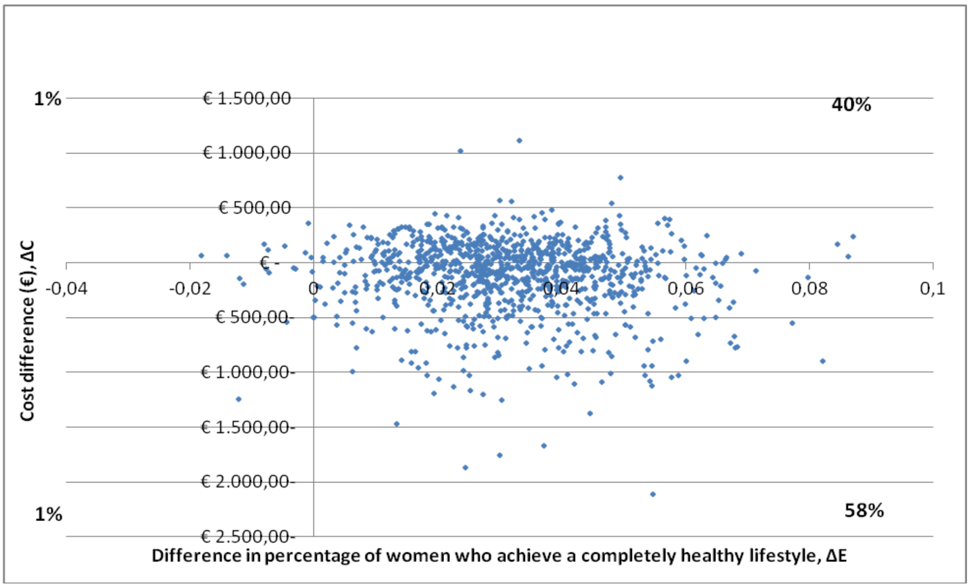



Figure 4 shows that all cost-effectiveness pairs are in the NE quadrant. This implies that there are more effects but also more costs. On average, women who use 'Slimmer Zwanger' have 3.1% higher probability than women who 'do nothing' to achieve a completely healthy lifestyle at €61 additional costs. The average ICER is €1823 per women who achieves a completely healthy lifestyle.

**Figure 5** *CE plane model 1 with outcome 'Completely healthy lifestyle' when the societal perspective is used*




From figure 5 can be derived that 'Slimmer Zwanger' can result in cost-savings, additional costs, health gains and health losses when societal perspective is used. Average incremental costs per women who achieved a completely healthy lifestyle are €-120, implying cost savings. The average ICER is €-11528 per women who achieves a completely healthy life.

**Figure 6.** *CEACsModel 1 Completely healthy lifestyle for 'Slimmer Zwanger'compared to 'do nothing'*

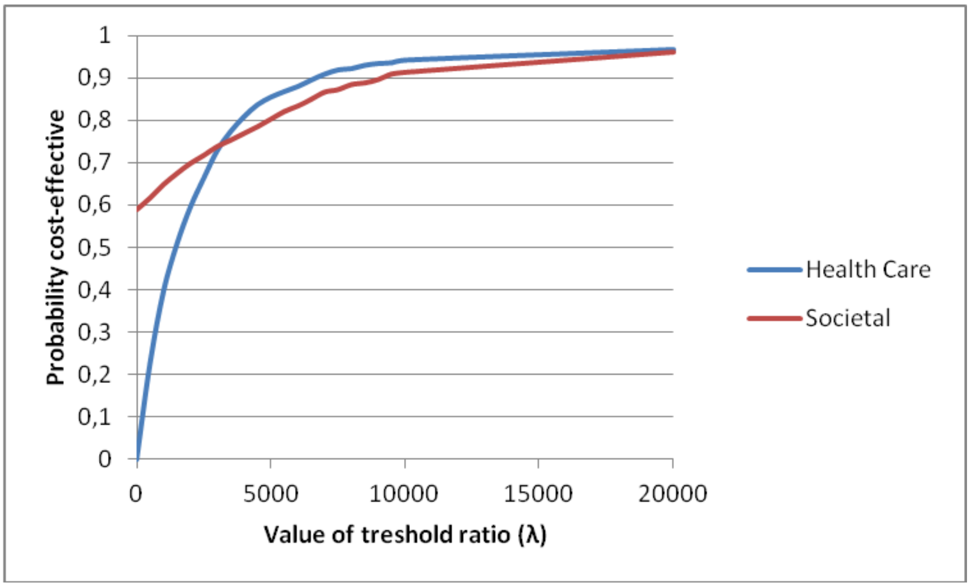
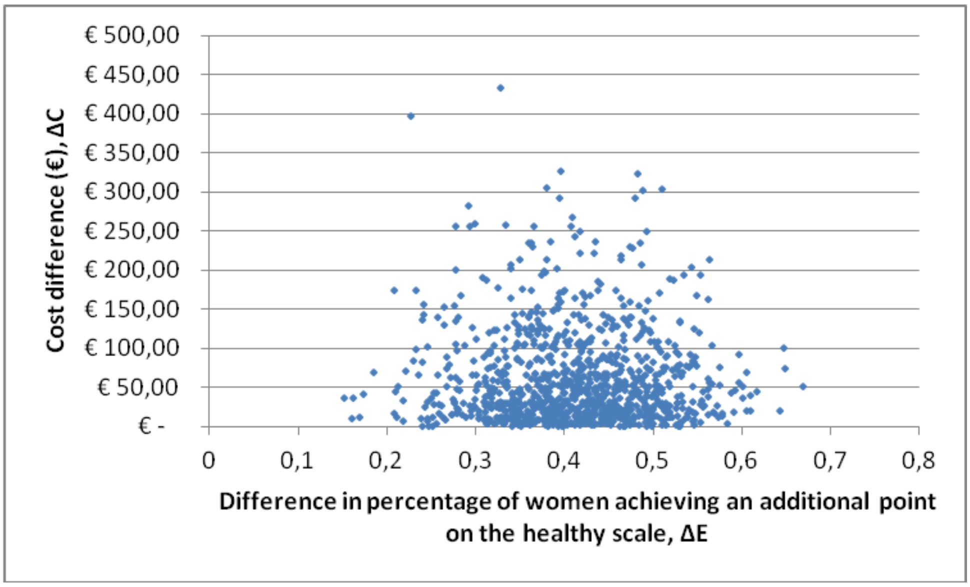



Figure 6 shows that when the health care perspective is used, there are no cost-savings, since the CEAC asymptotes to zero. The probability that 'Slimmer Zwanger' is more cost effective than 'do nothing' increases with an inceasing treshold (λ), however the CEAC will never asymptote to one as in some cases there are health losses.

When the societal perspective is used, the probability that 'Slimmer Zwanger' is more cost-effective than 'do nothing' is approximately 0.60 with a treshold of zero. In about 60% of the cases, 'Slimmer Zwanger' leads to cost savings. The probability increases as the treshold increases and will increase up to almost one since in very few (about 2%) of the cases there are health losses.

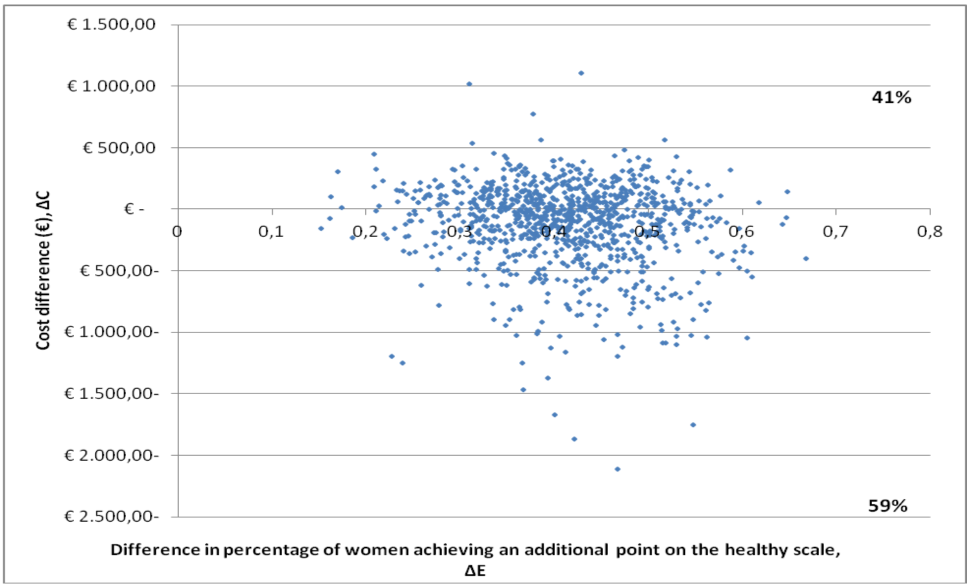
### *Model 1 Healthy Scale*

**Figure 7.** *CE plane model 1 with outcome 'healthy scale' when health care perspective is used*



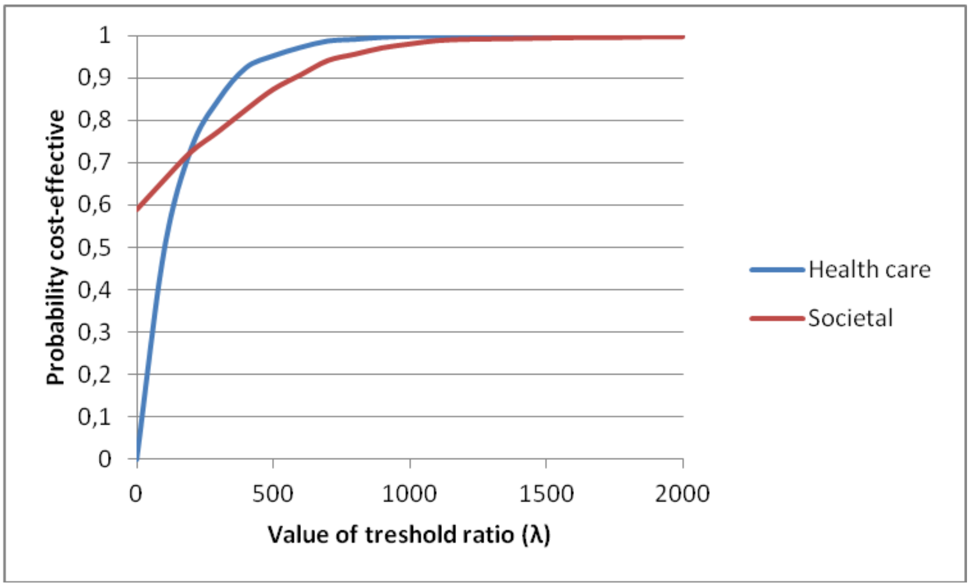

In figure 7 the results of the sensitivity analysis of model 1 with outcome 'healthy scale' are represented. All the cost-effectiveness pairs of the analysis lie in the NE quadrant, implying additional health benefits and additional costs. On average, women who use 'Slimmer Zwanger' score 0.421 points higher on the healthy scale than those who 'do nothing'. This at additional averge costs of €61 when the health care perspective is used. This results in a mean ICER of €157 per additional point on the healthy scale per women (reduction of one unhealthy lifestyle).

**Figure 8**. *CE plane model 1 with outcome 'healthy scale' when societal perspective is used*




When the societal persective is used the average additional effects of 0.421 are at average additonal costs of €-120, resulting in an mean ICER of €-277 per additional point on the healthy scale per women.

**Figure 9.** *CEACs model 1 'healthy scale' for 'Slimmer Zwanger'compared to 'do nothing'*

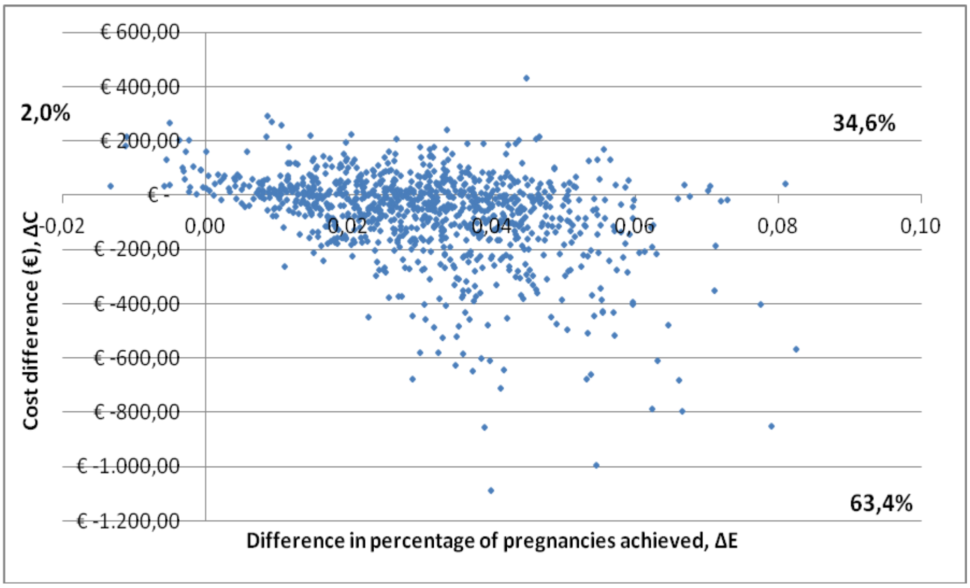



From figure 9 can be read, that when the health care perspective is used there are no cost-savings since the CEAC cuts the y-axis at zero. The entiry density involves health gains, therfore the CEAC is an increases function which asymptotes the y-axis to one. When society is willing to pay approximately €1000 (or more) for a reduction of one unheatlhy lifestyle per women, than 'Slimmer Zwanger' will always be more cost-effective than 'do nothing'.

From the societal perspective, in approximately 60% of the cases there will be cost-savings in terms of reduction in unheatlhy lifestyle behaviors. The probability that 'Slimmer Zwanger' is more effective than 'do nothing' increases with the treshold. There are never health losses since the CEAC cuts the y-axis at one.

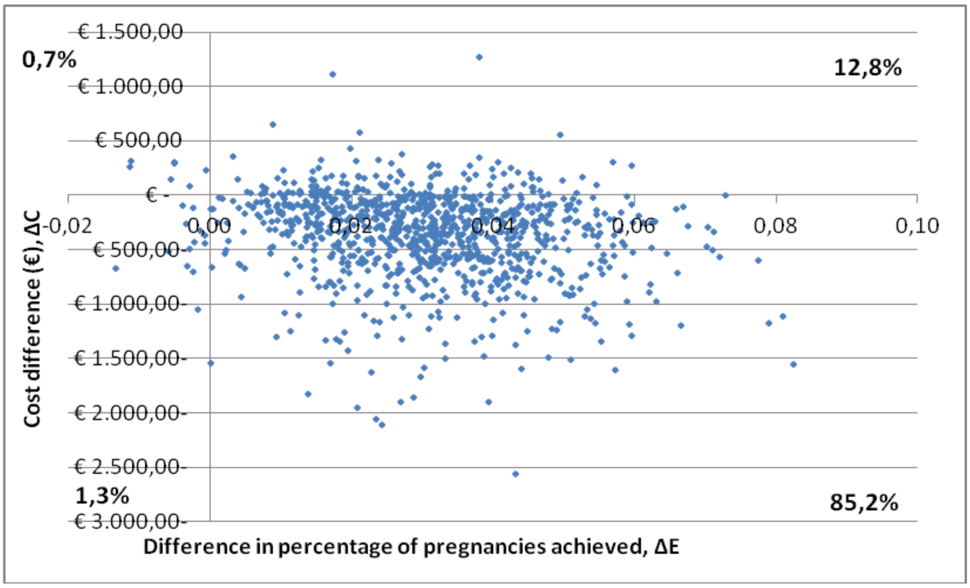
### *Model 2 Pregnancies Achieved*

**Figure 10.** *CE plane model 2 with outcome 'achieved pregnancies' when the health care perspective is used*



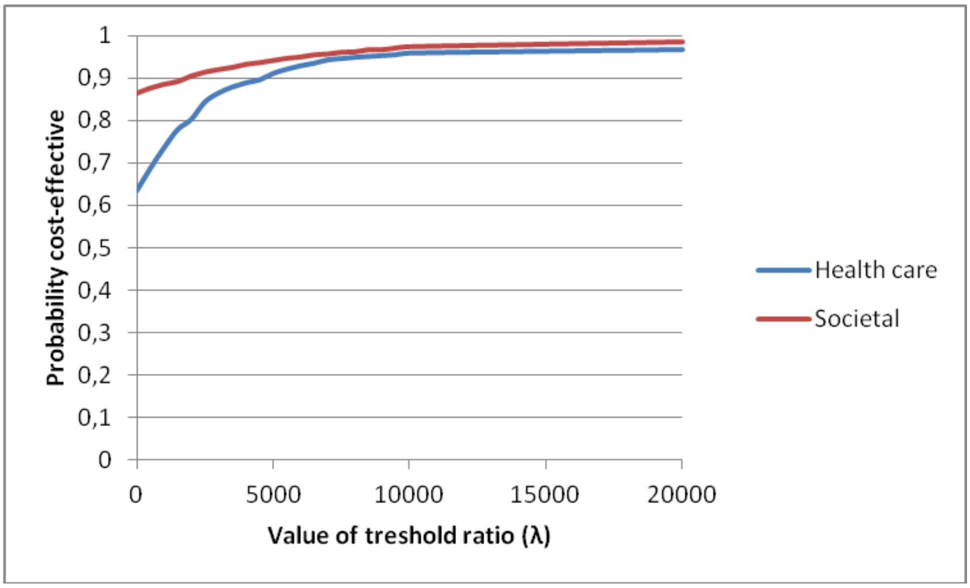

From figure 10 can be derived that when the health care perspective is used, there are either cost-savings, additional costs, health losses or health gains. Almost all cost-effectiveness pairs lie in the NE or SE quadrant. On average, 3% more pregnancies are achieved when 'Slimmer Zwanger' is used compared to 'do nothing' at additional costs of €-67.

**Figure 11.** *CE plane model 2 with outcome 'achieved pregnancies' when the societal perspective is used*



When the societal perspective is used, almost all-cost effectiveness pairs lie in the NE or SE quadrant. The additional effects are achieved at average costs of €362.

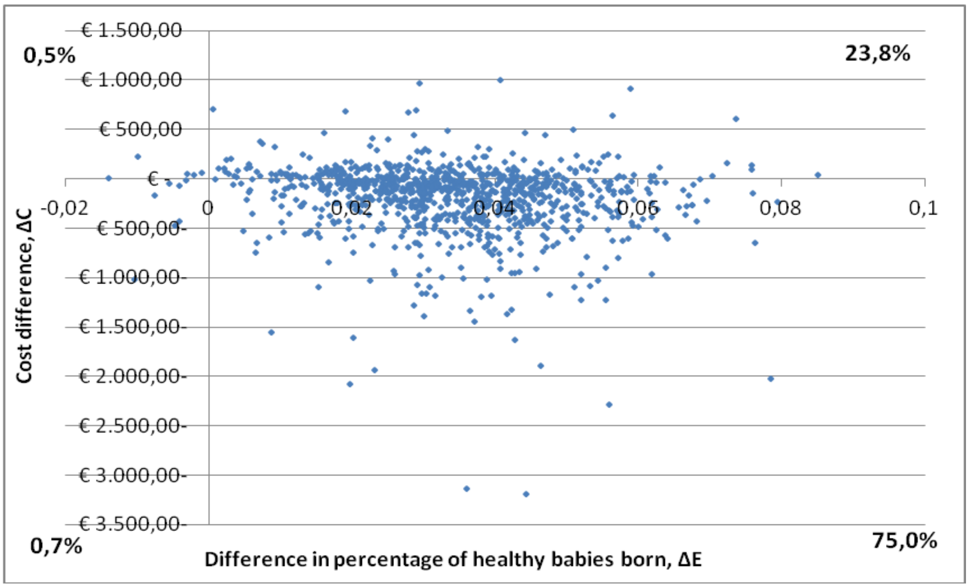
**Figure 12.** *CEACs model 2 for 'Slimmer Zwanger'compared to 'do nothing'*




From figure 12 can be derived, that the probability that 'Slimmer Zwanger' is cost-effective compared to 'do nothing' in terms of pregnancies achieved, is approximately 0.65 and 0.88 when the threshold is 0, from the heatlh care and societal perspective respectively. Both probabilities rise with an increasing treshold. Because in some, but very few, cases there are health losses, these probabilities will never reach one.

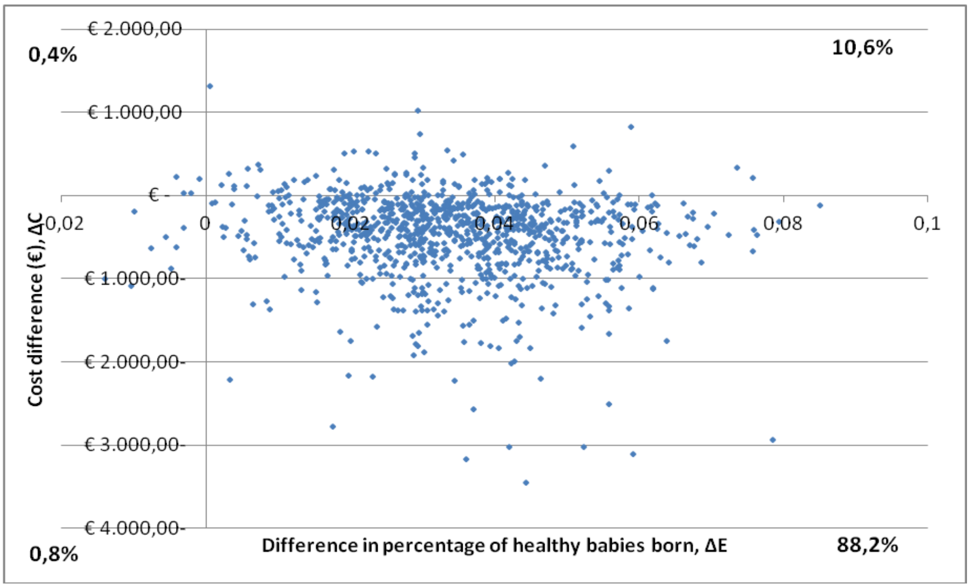
### *Model 3 Healthy Babies Born*

**Figure 13.** *CE plane model 3 with outcome 'healthy babies born' when the health care perspective is used*



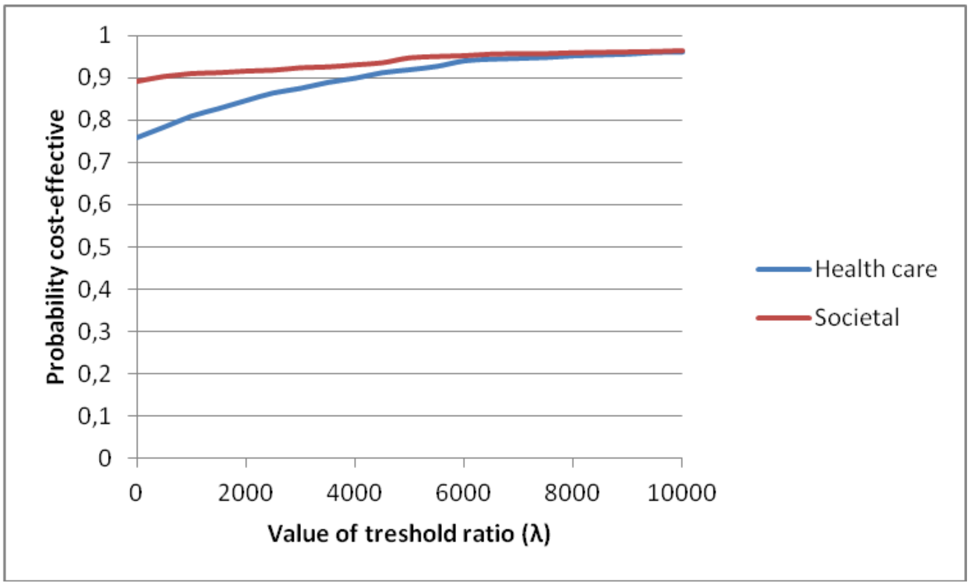
From figure 13 can be derived that when the health care perspective is used there are either cost-savings, additional costs, health losses or health gains when 'Slimmer Zwanger' is used compared to 'do nothing'. Almost all cost-effectiveness pairs are in the NE or SE quadrant. On average, 3.4% more healthy babies are born when 'Slimmer Zwanger' is used compared to 'do nothing' at average costs of €-196 and a mean ICER of €-4568 per healthy baby born.

**Figure 14.** *CE plane model 3 with outcome 'healthy babies born' when the societal perspective is used*




When the societal perspective is used, again almost all cost-effectiveness pairs lie in the NE or SE quadrant. The additional average costs are €-477 and the mean ICER is €-14213 per healthy baby born.

**Figure 15.** *CEACs model 3 for 'Slimmer Zwanger'compared to 'do nothing'*




From figure 15 can be derived, that the probability that 'Slimmer Zwanger' is cost-effective compared to 'do nothing' in terms of healthy babies born, is approximately 0.75 for the health care and 0.90 for the societal perspective when the treshold is zero. Both probabilities rise with an increasing treshold. Because in some, cases ther are health losses, these probabilities will never reach one.

**Table 10.** *Probabilistic sensitivity results: health care/societal perspective. Mean costs, mean effects, mean incremental costs, mean incremental effects, mean ICERs*

| | Perspective | Mean effect (95% CI) | Mean cost (€)(95% CI) | Mean incremental effect | Mean incremental cost (€) | Mean ICER (€/effect) |
|---|---|---|---|---|---|---|
| **Model 1 'Do nothing' Completely healthy** | Health care | 0.013 | 0 | | | |
| **Model 1 'Slimmer Zwanger' Completely healthy** | Health care | 0.044 | 61 | 0.031 | 61 | 1823 |
| **Model 1 'Do nothing' Completely healthy** | Societal | 0.013 | 1157 | | | |
| **Model 1 'Slimmer Zwanger' Completely healthy** | Societal | 0.044 | 1037 | 0.031 | -120 | -11528 |
| **Model 1 'Do nothing' healthy scale** | Health care | 2.477 | 0 | | | |
| **Model 1 'Slimmer Zwanger' healthy scale** | Health care | 2.889 | 61 | 0.412 | 61 | 157 |
| **Model 1 'Do nothing' healthy scale** | Societal | 2.477 | 1157 | | | |
| **Model 1 'Slimmer Zwanger'** | Societal | 2.889 | 1037 | 0.412 | -120 | -277 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **healthy scale** | | | | | | |
| **Model 2 'Do nothing'** | Health care | 0.435 | 2422 | | | |
| **Model 2 'Slimmer Zwanger'** | Health care | 0.465 | 2355 | 0.030 | -67 | 1612 |
| **Model 2 'Do nothing'** | Societal | 0.435 | 4037 | | | |
| **Model 2 'Slimmer Zwanger'** | Societal | 0.465 | 3675 | 0.030 | -362 | -47694 |
| **Model 3 'Do Nothing'** | Health care | 0.369 | 5204 | | | |
| **Model 3 'Slimmer Zwanger'** | Health care | 0.402 | 5008 | 0.034 | -196 | -4568 |
| **Model 3 'Do Nothing'** | Societal | 0.369 | 6778 | | | |
| **Model 3 'Slimmer Zwanger'** | Societal | 0.402 | 6302 | 0.034 | -477 | -14213 |

# Discussion

## *Main Findings*

In this study the cost-effectiveness of 'Slimmer Zwanger' was evaluated compared to 'do nothing'. The results ranged from intermediate to final outcomes, i.e. a reduction in unhealthy lifestyle behaviors, pregnancy probability and the probability of having a healthy baby. 'Slimmer Zwanger' is a preventive intervention that aims to improve the lifestyle of subfertile women in order to increase pregnancy probability and improve pregnancy outcomes for those who do become pregnant.

This modeling study showed that 'Slimmer Zwanger' can contribute to a reduction in unhealthy lifestyle behaviors of subfertile women; however there are costs associated with this when looking at it from a health care perspective. Acceptance of the program and whether 'Slimmer Zwanger' is cost effective compared to 'do nothing' will depend on what society is willing to pay for a reduction in unhealthy lifestyle behaviors. On the other hand, from a societal point of view, 'Slimmer Zwanger is expected to be cost-effective in terms of a reduction in unhealthy lifestyle behaviors with a probability of approximately 0.60.

Moreover, this study showed that 'Slimmer Zwanger' compared to 'do nothing' can increase the percentage of subfertile women who spontaneously become pregnant by making improvements in their lifestyle behaviors. 'Slimmer Zwanger' is expected to be cost-effective in terms of pregnancies achieved and has a probability of 0.65 and 0.88 from health care point of view and societal point of view respectively.

Finally, this study showed that by using 'Slimmer Zwanger' subfertile women who do become pregnant, have a higher chance of having a healthy baby by making improvements in their lifestyle behaviors. From a societal perspective, 'Slimmer Zwanger' is expected to be cost-effective with a probability of approximately 0.75 and from a health care perspective it has a probability of 0.90.

## *Strengths*

The first strength of this study is that it is the first to evaluate the cost-effectiveness of an e-health intervention that aims to improve several lifestyle behaviors of women who are trying to become pregnant. To our knowledge, only two studies exist that investigate the cost-effectiveness of preconception counseling through the use of the mobile phone (Dornelas et al., 2006; Parker et al., 2007). However, the interventions studied by these researchers only focused on smoking cessation and not other lifestyle behaviors. In addition, the interventions were based on phone calls instead of text messages. Furthermore, other research about the cost-effectiveness of preconception counseling to improve lifestyle behaviors is available. However, this preconception counseling did not target the subfertile population but women with diabetes mellitus and the interventions were based on visits to a clinic (Elixhauser et al., 1993; Kolu et al, 2013; Scheffler et al., 1992).

The second strength of this study is that the cumulative effect of multiple unhealthy lifestyle behaviors on pregnancy probability and pregnancy outcomes was studied. Only a few studies have used this approach to assess the effect of unhealthy lifestyle behaviors on pregnancy probability (Chavarro et al. 2007; Hassan & Killick, 2004). To our knowledge, there are no studies available that assess the cumulative effect of unhealthy lifestyle behaviors on pregnancy outcomes. In addition, there are no cost-effectiveness studies available that assess the reduction in unhealthy lifestyle behaviors on pregnancy and pregnancy outcomes. However, it appears extremely relevant to study the cumulative lifestyle behaviors since approximately 60% of the Dutch population has more than one unhealthy lifestyle behavior (Schuit et al., 2002). In addition, Hassan & Killick (2004) have demonstrated that conception probabilities in the general population consistently fell as the numbers of unhealthy lifestyle variables increased (0.82 with two-, and down to 0.38 with four unhealthy behaviors).

## *Limitations*

The costs-effectiveness analysis described in this study also has some important limitations that should be addressed. The general limitations are discussed in the following section, followed by the limitations regarding the three models and the sensitivity analysis.

### *General Limitations*

First, a decision tree to model the costs and effects of the intervention was used. The decision tree is a widely used technique in economic evaluations; however has the important limitation that it does not explicitly define time. Therefore, time dependent elements are difficult to implement (Drummond et al., 2005). For instance, in our models women can either change their behavior or not and either become pregnant or not. With the decision tree, we cannot present the possibility that women fall back into more unhealthy behaviors or become pregnant and cease to be pregnant (due to miscarriage). In the 'real world' it is expected that these things do occur. Therefore, using a Markov model instead of a decision tree, would have given a better reflection of the real world situation. The Markov model is more flexible and can handle the time related decision tree problems (Briggs et al., 2006; Drummond et al.,2005).

Second, a limited time horizon of one year was used. In economic evaluations it is necessary to choose a time horizon that is sufficiently long to reflect all key differences between alternatives in terms of costs and effects. (Briggs et al., 2006). The intervention 'Slimmer Zwanger' is a preventive intervention and for preventive interventions the preferred time horizon is in most cases a lifetime horizon as the aim of prevention is to increase the length of life and the quality of life of people (Owen et al., 2011; Van Baal et al., 2009). Therefore, it is expected that there are also costs and effects related to 'Slimmer Zwanger' that fall outside the chosen time horizon of one year. For instance, prevented diseases related to unhealthy lifestyle behaviors of women and their babies are not considered in our model.

The third limitation was that a Cost Effective Analysis (CEA) was used, in which the costs were related to the natural units of effect. Although CEA is commonly used in economic evaluation, they have the limitation that they can only inform decisions within single disease or intervention areas. Therefore, Cost Utility Analysis (CUA) in which generic outcomes, such as Quality Adjusted Life Years (QALY's), are the preferred measure of effect. QALY's combine survival with quality of life and make it possible to compare the cost-effectiveness of different interventions of different disease areas in order to inform decision making. However, it has been argued that the QALY is not an adequate measure to capture the impact of preventive interventions since the QALY focuses purely on health outcomes. In preventive interventions other non-health outcomes related to the quality of life are also important such as feeling of control, effort and overcoming an addiction. Therefore, QALY's can be expected to underestimate the effects of public health interventions when compared to medical interventions (Goebbels et al., 2011; Kelly et al., 2005; Lorgelly et al., 2010).

A fourth limitation of this study is that it is purely focused on cost-effectiveness and did not take equity concerns into account. As mentioned in the introduction, this is a general concern of economic evaluations of public health interventions. However, Hammiche et al. (2011) expect that couples with low education will benefit most from tailored personalized preconception counseling. In the Netherlands, individuals with low education often have unhealthier lifestyle behaviors (Busch & Schrijvers, 2010). Therefore, an additional beneficial effect of 'Slimmer Zwanger' might be that it can contribute to a reduction in health inequalities. Since this is an important goal of public health, incorporating equity considerations into the evaluation might increase the probability that this intervention would be cost-effective (Crombie et al.,2005).

Fifth, to measure the effects in terms of a reduction in unhealthy lifestyle behaviors, the survey data from the Erasmus MC was used. Although reductions in unhealthy behaviors were found, and it is expected that these were associated with the intervention, it is difficult to link causes and effects with only these data. A way to overcome this type of bias is by using a randomized controlled trial (Kelly et al., 2005). However, an RCT of 'Slimmer Zwanger' was not yet available but will be conducted in 2014. Another drawback of the survey data that was used is that the women surveyed were women from the general population and not from the subfertile population. Although the prevalence of unhealthy lifestyle behaviors is expected to be the same in the general and subfertile women, their motivation to change unhealthy behavior might differ (Hammiche et al., 2011). Subfertile women could be more motivated to change their behaviors when they are made aware that this will improve their chances to conceive. Therefore, the results of the survey might underestimate the actual behavioral changes of subfertile women. Furthermore, 'Slimmer Zwanger' is targeted at couples and this study only evaluated the effects in women, while the lifestyle behaviors of males also play an important role in the fertility of couples (Homan et al., 2007). In addition, it is assumed that the effectiveness of counseling is higher when targeted at couples than when targeted at women only (Hammiche, 2011).

Furthermore, the results of the survey revealed that 'Slimmer Zwanger' reduced the number of unhealthy lifestyle behaviors (table 1) but also the distribution of the specific unhealthy lifestyle behaviors within one unhealthy lifestyle behavior (table 2). For instance, a reduction in women who smoked was found when they used 'Slimmer Zwanger', however the number of women who had an unhealthy BMI increased after six weeks of using 'Slimmer Zwanger'. Whether this gives an accurate representation of reality is questionable. However, this is a limitation of representing the lifestyle behaviors cumulative as it is unknown how the unhealthy lifestyle behaviors within two to four unhealthy lifestyle behaviors are distributed. In addition, it is unknown which unhealthy lifestyle behavior women change when they have several unhealthy lifestyle behaviors.

The sixth limitation refers to the lifestyle behaviors included in the model. The following lifestyle behaviors were used; unhealthy BMI, no folic acid, lack of physical activity, insufficient vegetables and/or fruit, smoking. However, it could be argued that BMI is not a lifestyle behavior but a consequence of unhealthy lifestyle behaviors (lack of physical activity and unhealthy nutrition). In addition, it could be argued that folic acid use is part of nutritional behavior. Yet, BMI and folic acid were included in the model as separate lifestyles, since there is strong substantiation that these unhealthy lifestyle behaviors are associated with impaired fertility and adverse pregnancy outcomes (Ebisch et al., 2007; Homan et al., 2007; Shah & Ohlsson, 2009 et al., Stothard et al. 2009 ). In addition, folic acid use and BMI are both modifiable as the other lifestyle behaviors.

Finally, it is unknown how the specific lifestyle variables are distributed within two to four unhealthy lifestyle behaviors. It is known for instance, that not taking folic acid supplements has a far greater effect on fertility and pregnancy outcomes than a lack of physical activity. Therefore, it would be interesting to know the prevalence of combinations of unhealthy lifestyle behaviors, and which combinations are most common in those having two and more unhealthy lifestyle variables.

### *Limitations of Model 1*

For model 1, the probabilities were derived from survey data from the Erasmus MC. These data were recently obtained from the online survey of 'Slimmer Zwanger'. Since most observations were available at week six, we used these to derive the probabilities of the unhealthy lifestyle behaviors in the 'Slimmer Zwanger' population. However, the question remains whether women further improved their unhealthy lifestyle behaviors over time or fell back into old habits. Furthermore, the data did not contain information about alcohol consumption of the women and therefore it was not possible to include this in the model. However, there is sufficient substantiation that alcohol consumption affects fertility (Homan et al., 2007). In addition, approximately 90% of the reproductive population in the Netherlands drinks alcohol occasionally (Statistics Netherlands, 2010). Therefore, it would have been interesting to take alcohol consumption into account in the models.

There are also limitations with regard to the approach used to calculate the societal patient costs of model 1. These costs were calculated by combining several resources and assuming a positive linear relationship between the number of unhealthy lifestyles behaviors and costs. Admittedly, this approach gives a very rough estimation of the patient costs of those who have zero to five unhealthy lifestyle behaviors. To obtain more accurate estimations of the societal patient costs, it is recommended to use self reported 'cost diaries' (Goossens et al., 1999). For our study, this would imply that women who use 'Slimmer Zwanger' should keep a cost diary to keep track of all the costs they make with regards to their lifestyle. However, this would place a significant administrative burden on the women and therefore it is questionable whether this would be a feasible method.

### *Limitations of Model 2*

Some assumptions were made when structuring model 2 due to lack of literature. Most important was the assumption regarding the probability of becoming pregnant with a completely healthy lifestyle.

Although Hassan & Killick (2004) suggested that over 50% of subfertile couples who have one or several unhealthy lifestyle behaviors would conceive when they lead a completely healthy lifestyle, to our knowledge no actual numbers about this probability are represented in the literature. Therefore, a probability of 0.65 for subfertile women to become pregnant was assumed. This assumption was based on the opinion of an expert (R.P.M. Steegers-Theunissen, personal communication). Asking for an expert opinion is a legitimate method for assessing probabilities when objective estimates are not available. However, to guaranty the validity of the decision analysis and reduce the possibility of individual bias, it is preferred to use a group of experts rather than one single expert. A commonly used approach for this is the Delphi method which aims to obtain consensus of a panel of experts (Hunink et al., 2001; Weinstein et al., 2003). Since the probability of pregnancy with a completely healthy lifestyle also affects the probabilities of pregnancy with several unhealthy lifestyle behaviors, an approach that reduces the possibility of bias would have been preferred.

The probabilities of pregnancy with two or more unhealthy lifestyle behaviors were calculated by using RRs that were obtained from the paper by Hassan & Killick (2004). However, there are a number of limitations with regard to the use of these data for our model. First, the population studied by Hassan & Killick (2004) was not comparable to our selected population as they studied the general population while our study focused on the subfertile population. Second, Hassan & Killick (2004) used other unhealthy lifestyle behaviors to calculate the cumulative unhealthy lifestyle behaviors i.e. women's smoking > 15 cigarette's each day, men's smoking > 15 cigarette's each day, men's alcohol consumption > 20 units each week, women's coffee and tea consumption ≥ 7 cups each day, women's weight > 70 kg, social deprivation score > 60, women's age > 35 years, and/or partner age > 45 years at time of conception. Since the study of Hassan & Killick (2004) is one of few that investigated the cumulative effect of multiple unhealthy lifestyle behaviors on pregnancy probability, we used the Relative Risks (RRs) and assumed our selected population and unhealthy lifestyle behaviors were comparable to those of Hassan & Killick (2004).

Furthermore, the literature used to calculate the probabilities of the separate lifestyle behaviors (BMI, no folic acid, lack of physical activity, insufficient vegetables and/or fruit, smoking) described the RR/ORs of pregnancy with the specific unhealthy lifestyle behaviors after fertility treatment. These were used even though our study was focused on the chance of spontaneous pregnancy of the subfertile population (without fertility treatment). To our knowledge no evidence is available that describes the chance of pregnancy with the specific lifestyle behaviors. Therefore, it was assumed that the risks of ongoing pregnancy with the specific unhealthy lifestyles obtained from the literature were comparable to those of spontaneous conception without fertility treatment.

Finally, for model 2 it was assumed that all women will undergo fertility treatment when they do not become pregnant, it is questionable whether this is true. In addition, only IVF costs were considered although there are also other types of fertility treatments available that might have other costs. Furthermore the costs of only one cycle of IVF treatment were considered even though the success rate after one cycle of IVF is only 25% (Malizia et al., 2009). Therefore, the costs of those who undergo fertility will in reality be higher.

### *Limitations of Model 3*

For model 3, objective estimates of the probabilities of having a BIG3 baby with a healthy lifestyle and several unhealthy lifestyle behaviors were absent. Therefore assumptions were made. First, the literature states that in the general population, the prevalence of BIG3 is 13.6%. Because the average number of unhealthy lifestyle behaviors in the general population was unknown, it was assumed that the general population has an average of two unhealthy lifestyle behaviors. This was a rough estimation, however when the average unhealthy lifestyle behaviors of the surveyed women were calculated, an average of 2.5 unhealthy lifestyle behaviors was found. Therefore, this assumption is expected to be conservative.

To calculate the probabilities of one, three, four and zero unhealthy lifestyle behaviors an OR of 1.3 was used. This was based on the estimation of an expert (Steegers-Theunissen, personal communication). Although a conservative approach was used in this estimation, using a formal method to derive expert estimates would have been preferred (as mentioned earlier).

The estimated costs of model 3 were based on a study from the United States. The costs were converted to euro's using the current exchange rate; however purchasing power parities are preferred as these take into account differences in purchasing power (Hakkaart van Royen et al., 2010). In addition, only health care costs of newborns were included and not the additional costs that the mothers might make due to adverse pregnancy outcomes. Furthermore, societal costs of adverse pregnancy outcomes were not included into our model. However, Hodek et al. (2011) have suggested that these costs are very important in decision-making as financial and emotional burdens on families are significantly increased with adverse pregnancy outcomes.

Although the costs related to model 3 are a quite rough estimation as opposed to an exact estimate, it is known that costs related to hospital stay for newborns are very high. In addition, the costs that were used in this study are more likely to be an underestimation than an overestimation of the actual cost as maternal and societal costs were not included.

### *Sensitivity Analysis*

A probabilistic sensitivity analysis was performed in order to deal with the uncertainties as this is the recommended method in cost-effectiveness studies. However, some problems were encountered while attempting to fit the beta distributions, since the probabilities of model 2 and 3 were based on estimates and therefore the counts of events (α), the sample sizes (β=n-α) and standard deviations were not available. In order to obtain an estimation of the α's and β's, the probability was used and multiplied by 100 as estimates of α and 100- α as estimates of β . This might affect the result of the sensitivity analysis.

## *Comparing the Results with the Literature*

This study is the first to evaluate the cost-effectiveness of an e-health intervention aimed at reducing unhealthy lifestyle behaviors in subfertile women. Some research about the cost-effectiveness of preconception counseling to improve unhealthy behavior does exist, however is scarce.

For instance, two studies exist that evaluate the cost-effectiveness of telephone based counseling to reduce smoking behavior in women (Dornelas et al., 2006; Parker et al., 2007). One of these found the program to be cost-effective through significant reduction in smoking rates in women, the other was only moderately positive. In addition, a couple of other studies exist that evaluate preconception counseling that is targeted at women with diabetes mellitus (Herman et al., 1999; Scheffler et al., 1999; Elixhauser et al., 1993). Most of these studies reported costs-savings in favor of preconception counseling. The cost-savings they found mostly resulted from prevented adverse pregnancy outcomes related to diabetes mellitus (Elixhauser et al., 1993; Herman et al., 1999; Scheffler et al., 1992). On the contrary, two recent cost-effectiveness studies of a prevention program for

Gestational Diabetes Mellitus (GDM) through intensive dietary and physical-activity counseling, found these not to be cost-effective (Kolu et al. 2013; Oostdam et al., 2012).

However, results from these previous studies are not comparable to the results found in this study because their interventions differed from the intervention evaluated in this current study. None of the previous studies evaluated an intervention which aims to reduce several unhealthy lifestyle behaviors or used counseling through text messages. In addition, the populations studied differed from the population of this studied. None of the interventions mentioned were targeted at the subfertile population.

### *Generalisability of the Findings*

The findings from this study cannot be generalized to general population, since only subfertile women were evaluated. The survey data included women from all over the Netherlands; however the women have signed in for the program themselves, this may have led to selection bias. Therefore it is questionable whether the results can be generalized to the all subfertile women in the Netherlands.

### *Future Research Recommendations*

To construct the model for this cost-effectiveness study it was necessary to make a number of assumptions. This is because the evidence needed was not available. Therefore, additional research in this area is required.

The most notable aspect was that very little literature is available that describe the effects of cumulative unhealthy lifestyle behaviors in women on fertility and pregnancy outcomes. However, this seems to be extremely relevant as more and more women have several unhealthy lifestyle behaviors and not just one. In addition, not much is known about pregnancy probability when women lead a completely healthy lifestyle. More research in this area is required especially with regards to combinations of unhealthy lifestyle behaviors which are already known to individually influence fertility and pregnancy outcomes.

Furthermore, evidence about the probability of spontaneous conception in subfertile women through reductions in unhealthy lifestyle behaviors is not yet available. It is known that lifestyle behaviors have a great influence on reproductive health. Therefore, research about this would be an interesting addition to the current literature and might generate more support for preconception care.

Additionally, to our knowledge no evidence is available that describes the influence of lifestyle on pre-term birth, low birth weight and birth defects, as a combined outcome (BIG3). It seems useful to consider what the risk is of BIG3 as these are a major cause of perinatal mortality and morbidity in the Netherlands and occur in approximately 16% of pregnancies (Bonsel et al., 2010). Further research in this area is needed.

Moreover, not much evidence is currently available about the influence of personalized coaching trough e-health on lifestyle modification. However, this seems to be relevant as mobile technology is advancing rapidly as is the dependence of people on their mobile phones (Rizvi et al., 2011). This creates opportunities for, among others, more effective preventive health care aimed at lifestyle modification. Therefore, more research should be devoted to this, ideally with the use of randomized controlled trials.

From 2014 onward, a Randomized Controlled Trial of ‘Slimmer Zwanger’ will be performed with couples living in Rotterdam. A first next step in modeling the cost-effectiveness of ‘Slimmer Zwanger’ could be to use the data of this RCT as evidence of effectiveness of reduction in unhealthy lifestyle behaviors. In addition, an important next step would be to evaluate the long term cost-effectiveness of ‘Slimmer Zwanger’. This is of more interest to decision makers as the aim of preventive interventions is to increase the length of life and the quality of life of individuals.

## Conclusion

The objective of this thesis was to evaluate the cost-effectiveness of an innovative e-health intervention 'Slimmer Zwanger', which is aimed at improving the lifestyle behaviors of subfertile women and through this improving fertility and pregnancy outcomes. The intervention was compared to 'do nothing' and a decision analytic model was used to estimate the costs, effects and cost-effectiveness of this intervention on a range from intermediate to final outcomes i.e. reduction in unhealthy lifestyles, pregnancies achieved and healthy babies born. Several assumptions were made to construct the model. Based on these assumptions, the results of this study reveal that 'Slimmer Zwanger' is cost-effective compared to 'do nothing' in terms of reduction in unhealthy lifestyle behaviors, pregnancies achieved and healthy babies born when analyzed from the societal perspective. From the health care perspective, 'Slimmer Zwanger' is cost-effective compared to 'do nothing' in terms of pregnancies achieved and healthy babies born. However, in terms of reduction in unhealthy lifestyle behaviors more effects but also more costs are expected.

### *Policy Interpretations*

Aim of economic evaluations in health care is to support decision-makers in making efficient and equitable decisions (Brazier et al., 2007). Crucial question which arises from our study is therefore; should 'Slimmer Zwanger' be adopted on the basis of the existing evidence? Although this study has some significant limitations that increase the uncertainty of the outcomes of the study, there are several reasons to expect that 'Slimmer Zwanger' is a good investment.

To start with, our modeling study and previous research revealed that through improvements of unhealthy lifestyle behaviors, reductions in subfertilty and adverse pregnancy outcomes can be expected. However, whether these results can be achieved depends primarily on the motivation of women to change their behavior. 'Slimmer Zwanger' is simply a tool that provides women with information and feedback on health behaviors, but women do have to take their own responsibility in order to truly modify their unhealthy behaviors. Although the survey results of 'Slimmer Zwanger' show reductions in unhealthy lifestyle behaviors of women in the general population and better results are expected in a more motivated subfertile population, we do realize that using a survey is not the strongest study design to show effectiveness. However, even if these behavior changes do not occur through the use of 'Slimmer Zwanger', it is important to make the reproductive population and especially those with fertility problems more aware of the effects of their unhealthy lifestyle behaviors on reproductive health. It is also important that woman understand their own responsibility regarding this issue since the prevalence of unhealthy lifestyle behaviors is high and generally the knowledge about the effects of these risk factors is low (Hammiche et al., 2011). 'Slimmer Zwanger' is therefore a good opportunity to make subfertile women more aware and emphasize their own responsibility in their reproductive health.

Furthermore, it could be emphasized that the assumptions made to construct our model affect the outcomes in terms of the percentage of pregnancies achieved in subfertile women and healthy babies born. Nevertheless, this study showed that the probability that 'Slimmer Zwanger' is cost-effective is very high on different outcomes as low costs are related to this intervention and high costs can be prevented. Even when effects are in reality smaller, it is still expected that favorable cost-effectiveness ratios will be found. In addition, even if our models give overestimations of the effects, it is still important for subfertile women to improve their lifestyle behaviors as improving lifestyle has also other beneficial effects that are not included in our models. For instance, a healthy nutrition improves the chance of pregnancy after fertility treatment (Twigt et al., 2012). Furthermore, a healthier lifestyle in subfertile women as is in the general population, is important for the own health, longevity and quality of life. The preconception period is often seen as a good period to intervene as women and couples are more motivated to change their behavior in this period (Phelan, 2010). Despite this, few preconception initiatives are available in the Netherlands. Provide 'Slimmer Zwanger' for the subfertile population would be a good step forward.

Outcomes of this study were not represented in a general outcome measure such as the QALY. Therefore the results of our study are not comparable to other interventions for other diseases. However, previous studies have shown that subfertility and adverse pregnancy outcomes have a substantial negative impact on the experienced Quality of Life (QoL) and health related Quality of Life of couples and especially of women (Chachamovich et al. 2010; Hodek et al., 2011; Monga et al., 2004). Therefore it is expected that costs savings will also be found when the QALY is used as outcome measure instead of natural units of effects. When an intervention is cost saving, this implies fewer cost and more effects. This will always be good value for money.

Furthermore, a limited time horizon of one year was chosen for this study, where a live time horizon is preferred in evaluating preventive interventions. Additional research can be done to assess the cost-effectiveness when costs and effects over a longer time horizon are taken into account. However, it is not expected that a longer time horizon will negatively affect the results found by this study. Not much additional costs related to the intervention are expected when a longer time horizon is chosen. In contrast, long-term health benefits of a healthier lifestyle can be expected. Therefore a longer time horizon is expected to result in a more favorable incremental cost effectiveness ratio of 'Slimmer Zwanger' compared to 'do nothing'.

In conclusion, it is desirable to implement the 'Slimmer Zwanger' intervention for subfertile women.

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