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HEALTH ECONOMIC EVALUATIONS IN THE CONTINUUM OF CHRONIC DISEASE PREVENTION

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Abbreviations

BC	Breast Cancer
BCC	Basal Cell Skin Cancer
BMI	Body Mass Index
CEAC	Cost-Effectiveness Acceptability Curve
CHD	Coronary Heart Disease
CNCD	Chronic Non-Communicable Disease
CRC	Colorectal Cancer
DALY	Disability-Adjusted Life-year
EBRB	Eenergy Balance-Related Behaviour
EQ-5D	EuroQol 5 Dimensions
GDP	Gross Domestic Product
HiAP	Health in All Policies
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
LDS	Lesion-Directed Screening
MSC	Melanoma Skin Cancer
NICE	National Institute for Health and Care Excellence
NMSC	Non-Melanoma Skin Cancer
OECD	Organisation for Economic Co-operation and Development
PHE	Public Health Expenditure
PSA	Probabilistic sensitivity analysis
QALY	Quality-Adjusted Life-Year
RR	Relative Risk
RRR	Relative Risk Reduction
SCC	Squamous Cell Skin Cancer
SSB	Sugar-Sweetened Beverage
TBE	Total Body Examination
UV	Ultraviolet
WHO	World Health Organization

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Part 1: General introduction

1.1. Chronic diseases: definition and burden

Chronic diseases are defined as diseases of long duration and generally slow progression (WHO, 2005a). Chronic diseases are commonly used as a synonym for non-communicable diseases, denoting diseases that are not passed from one person to another. However, some communicable diseases (i.e. infectious diseases) can be chronic too, for example HIV infection. In this PhD-thesis, chronic diseases will be defined as Chronic Non-Communicable Diseases (CNCDs). The World Health Organization (WHO) addresses four major CNCDs, considered to have the highest share in CNCD morbidity and mortality[1], namely cardiovascular disease (mainly coronary heart disease and stroke), cancer, chronic respiratory diseases (such as chronic obstructive pulmonary disease, asthma, pulmonary hypertension) and diabetes (WHO, 2014a). Mental disorders, such as depression or anxiety disorders, are generally not included in the concept of CNCDs, although these disorders have a large impact on society as well, in terms of population health and public expenditure (Lokkerbol et al., 2013). The disease burden associated with mental disorders is largely attributable to disability rather than mortality (Figure 1). In Belgium, 20% of the population uses psychotropic drugs (Van Herck & Van de Cloot, 2013). Besides, although not directly related to mortality, mental disorders, particularly depression and schizophrenia, are the major determinant of suicide (Ferrari et al., 2014; Harris & Barraclough, 1998; WHO, 2004). Half of the people with suicidal thoughts suffer from a mental disorder (Nock et al., 2009). Because of their high burden, some health scientists argue for mental disorders to be classified as one of the main types of CNCDs (Ivbijaro, 2011; Ngo et al., 2013). Therefore, in this PhD-thesis, the concept of CNCDs also includes mental disorders, unless otherwise stated.

CNCDs are major contributors to the global burden of disease (Vos et al., 2015; WHO, 2014a). The burden of disease concept can be described as the impact of a health problem on an individual or a population usually measured by mortality and morbidity (called health burden) or the financial impact (called economic burden).

1.1.1. Health burden

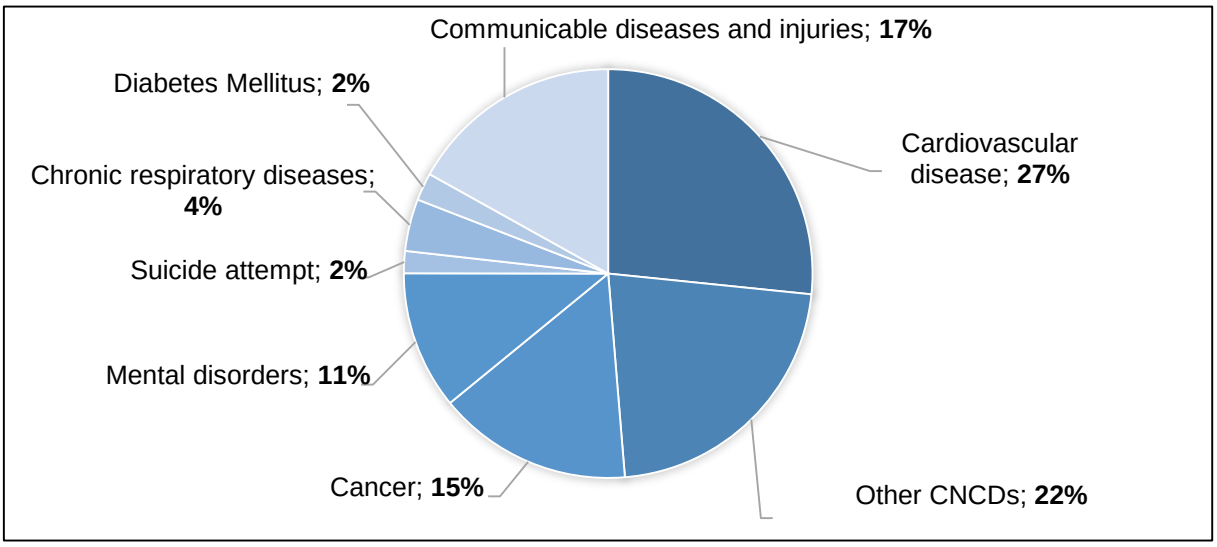
Many measures are available to assess the health of a population, such as disease prevalence, disease incidence, mortality, life-expectancy, etc. Summary measures of population health are measures that combine information on mortality and morbidity to represent the health of a particular population into one single number (Field & Gold, 1998). A wide array of summary measures have been proposed, for example disability-free life expectancy, disability-adjusted life expectancy, health-adjusted life expectancy, or disability-adjusted life years (Murray, Salomon, & Mathers, 2000). The WHO measures the global health burden using the summary measure of disability-adjusted life year (DALY)[2]. The European burden of disease in 2012 consisted of 314,387,085 DALYs, or 348 DALYs per 1,000 people,

[1] Morbidity data indicate the number of persons in a population who become ill (incidence) or are ill at a given time (prevalence) (Centers for Disease Control and Prevention, 2016b) Mortality data indicate numbers of deaths by place, time or cause (WHO, 2016c)

[2] DALYs are calculated as the sum of years of life lost due to early mortality and years lived with disability due to the disease or its consequences. As such, the DALY concept includes life-expectancy, disease incidence/prevalence, disability weight and average duration of the condition until death.

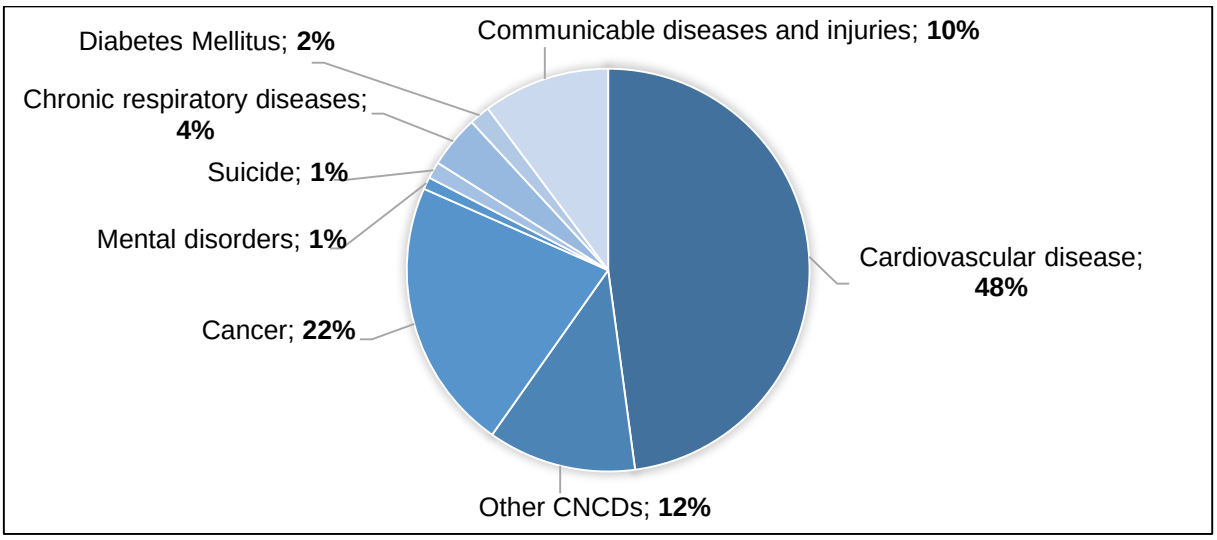
of which about 81% was due to CNCDs (Vos et al., 2015; WHO, 2014a) (Figure 1a). When expressing the burden in terms of mortality, CNCDs account for 88% of all deaths in Europe (WHO, 2014b) (Figure 1b).

Figure 1a: Proportions of causes of DALYs in Europe, 2012



CNCDs: Chronic Non-Communicable diseases; Source: (WHO, 2014a)

Figure 1b: Proportions of causes of deaths in Europe, 2012



CNCDs: Chronic Non-Communicable diseases; Source: (WHO, 2014b)

Overall, the figures for Belgium are in line with the European average. The global disease burden is slightly lower than the European average (295 versus 348 DALYs per 1,000 persons), but the proportion of CNCDs within the global disease burden (85%) is slightly higher (WHO, 2012b). As CNCDs (except for mental disorders) especially develop at older age and as population is ageing[3], an increase in CNCDs

[3] According to the projections of the Organisation for Economic Co-operation and Development (OECD), by 2050 the number of people aged 65 years or over will have increased by one third, resulting in a proportion of about 25%-30% of the total population

can be expected for the coming decades. Currently, about 17% of the population in Europe aged 65+ suffers from diabetes and 46% from heart or blood pressure problems (Eurostat, 2015a). According to the Belgian Health Survey in 2013 (Scientific Institute of Public Health, 2013), one third of the Belgian population aged between 30 and 100 suffers from a longstanding illness, chronic condition or handicap.

1.1.2. Economic burden

Beside morbidity and mortality due to diseases, the burden of disease concept should be completed with a consideration of the economic impact on society in general and more specifically on the public health budget. Generally, according to an estimation of the European Union, currently 70 to 80% of a country's total health expenditure is spent on treating chronic diseases (European Union, 2014). Assessing the economic burden of disease more in detail implies exploring the financial consequences of the disease, for the patient, employers, government or the society at large. Results of such economic burden of disease studies provide insight into the overall magnitude of economic losses and the key cost drivers, informing policy makers on the priority-setting of health interventions. Research guidelines usually recommend to use the societal viewpoint in cost-assessment studies, meaning that costs for the society at large should be addressed, including medical costs, as well as costs borne outside the health care sector, such as productivity losses and patient travel expenses (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 2015; Jonsson, 2009). The report on the global economic burden of CNCDs, published by the World Economic Forum and the Harvard School of Public Health (Bloom et al., 2011), stated that CNCDs have a considerable financial impact of which cardiovascular disease and mental health disorders are the dominant contributors. The total cost of cardiovascular disease in Europe, from a societal perspective, was assessed at €214 billion in 2015 (€169 billion in 2003[4]), of which 62% were health care costs, 21% costs due to productivity loss and 17% informal care costs (i.e. opportunity cost of unpaid care) (Leal, Luengo-Fernandez, Gray, Petersen, & Rayner, 2006). The cost of depression in Europe – currently one of the major mental disorders – has been estimated to be €146 billion in 2015 (€118 billion in 2004[4]) of which 36% health care costs and 64% costs due to productivity loss (Sobocki, Jonsson, Angst, & Rehnberg, 2006). The total cost of cancer in Europe in 2015 was estimated to be €139 billion (€126 billion in 2009[4]), of which 40% were health care costs, 41% were costs due to productivity loss and 19% were informal care costs (Luengo-Fernandez, Leal, Gray, & Sullivan, 2013). Lung cancer had the highest share in the total cost due to cancer, followed by breast cancer, colorectal cancer and prostate cancer.

From the figures on the health as well as economic burden of CNCDs, it can be stated that these diseases put a high burden on society. This disease burden is expected to increase in the coming years, as the health burden, and as such the associated cost is estimated to double by 2030 (Atun et al., 2013).

[4] Adjusted for inflation based on the Harmonised Indices of Consumer Prices (Eurostat, 2016)

1.2. Prevention in the domain of public health

Promoting interventions to prevent and control CNCDs is important in order to lessen their impact on population health as well as on the public budget (WHO, 2015a), and is the main mission in the field of public health. Public health is defined as “all organised measures (whether public or private) to prevent disease, promote health, and prolong life among the population as a whole. Its activities aim to provide conditions in which people can be healthy and focus on entire populations, not on individual patients or diseases.“ (WHO, 2016e).

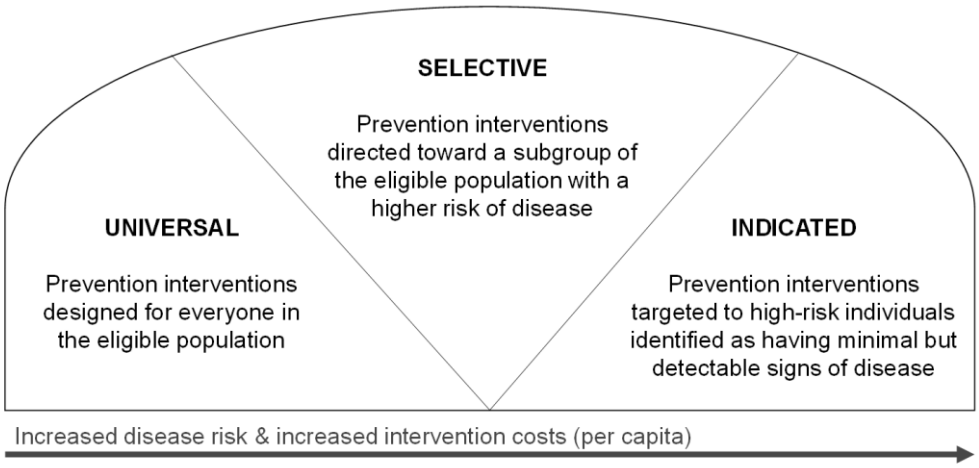
1.2.1. Classification of prevention interventions

Public health prevention interventions to manage and control CNCDs can be classified in several categories. The original public health classification of disease prevention was established by the Commission on Chronic Illness (1957) and adopted by other organisations, such as the World Health Organization (WHO) (2016f). It classifies prevention as primary, secondary or tertiary. Primary prevention tries to avoid the occurrence of an event/disease by reducing exposure of individuals to risk factors or by increasing their resistance to them. Secondary prevention is designed to reverse or retard progression of an existing condition and tertiary prevention is the management of a disease to prevent progress or recurrence, by treatment and rehabilitation programs. Although the goals of these three types of prevention appear to be straightforward, in practice this distinction is not always clear and overlap is common.

According to Gordon (1983) this classification depends on a clear identification of the biologic origin of the particular disease. While the relation between cause and development of acute infections and injuries may be obvious, this is not the case for CNCDs which currently constitute the major cause of disability and death. Therefore, he proposed an alternative classification more closely linked to the practical considerations related to the application of prevention interventions. His classification was based on a benefit-risk point of view in that the probability of getting a disease must be weighed against the cost and risks of the prevention intervention. Therefore, he proposed three categories, representing the population groups to whom the interventions were directed and for whom they were thought to be most optimal: universal, selective and indicated prevention (Figure 2). These levels denote preventive interventions that are oriented respectively towards the whole population, those who are at increased risk of a disease or health problem, and those who already show signs of developing a disease or health problem. *Universal prevention* is the most generally applicable type, which is desirable for everybody. This category comprises all those measures that can be implemented for the general public and which, in many cases but certainly not all, can be applied without much professional advice or assistance. An example is a school-based program for the promotion of an adequate diet, delivered to e.g. all preshoolers in the school, a policy measure such as a sugar tax, or a media campaign for the promotion of change in sedentary behaviour,…. Because of the balance of benefits against risks and costs, some prevention interventions are recommended for only a subgroup of the population which is based on specific characteristics such as age, sex, occupation or other characteristics related to an increased risk. These interventions can be classified as *selective prevention*. An example is a systematic screening

program with an age-restricted target population. A third category is *indicated prevention*, which applies to those persons who manifest a risk factor, condition or abnormality, that identifies them individually as being at high risk for development of a disease. Indicated prevention interventions are usually quite intense for the receiving person and can induce high costs per person. An example of indicated prevention is the management of hypertension or annual check-ups for patients in whom a skin cancer lesion has been removed. Gordon's classification applied only to asymptomatic individuals. He defined prevention as "measures, actions, or interventions that are practiced by or on persons who are not, at the time, suffering from any discomfort or disability due to the disease or condition being prevented". Nevertheless, in this thesis the view of the Institute of Medicine is adopted (Mrazek & Haggerty, 1994), in that indicated prevention interventions can apply to asymptomatic individuals with markers as well as to symptomatic individuals having minimal but detectable symptoms. For example, suicide prevention interventions might reduce the duration of the period one experiences early symptoms of suicidal thoughts and as such halt the progression of the severity of these thoughts to prevent the act of suicide.

Figure 2: Classification of public health prevention interventions



1.2.2. Management and control of chronic non-communicable diseases

Table 1 shows the age-standardised incidence and mortality rates for some important CNCDs in Europe and Belgium, of which the situation is worse in Belgium, compared to the European average. The (fatal) suicide rate, incidence- and mortality rate for breast cancer and colorectal cancer as well as the mortality rate for lower respiratory diseases is higher in Belgium than in Europe (Ferlay et al., 2013; OECD, 2012d; WHO, 2012a), arguing for further prevention research and interventions. In Belgium, but also globally, health goals are being formulated and action plans are being developed with the aim of reducing the morbidity and mortality due to CNCDs (Centers for Disease Control and Prevention, 2016a; Vlaams Agentschap Zorg & Gezondheid, 2016; WHO, 2016b). These goals and action plans all mention two main strategies, namely focussing on the modifiable risk factors of CNCDs and early detection of the disease.

Table 1: Age-standardised incidence and mortality rates in Belgium and Europe (per 100,000, in %), for the major CNCDs for which the rate was higher in Belgium than in Europe (2012)

	Suicide rate	Breast cancer incidence rate	Breast cancer mortality rate	Colorectal cancer incidence rate	Colorectal cancer mortality rate	Chronic lower respiratory disease, mortality rate
Belgium	17.4	147.5	29.5	M: 67.5; F: 43.4	M: 23.8; F: 15.3	46.2
EU average	13.3	108.8	22.4	M: 59; F: 36.1	M: 23.8; F: 14.2	34.9

Incidence rate: number of new cases of the disease in the particular population, during 2012, per 100,000 persons.

Mortality rate: measure of the number of deaths, in the particular population, during 2012, per 100,000 persons

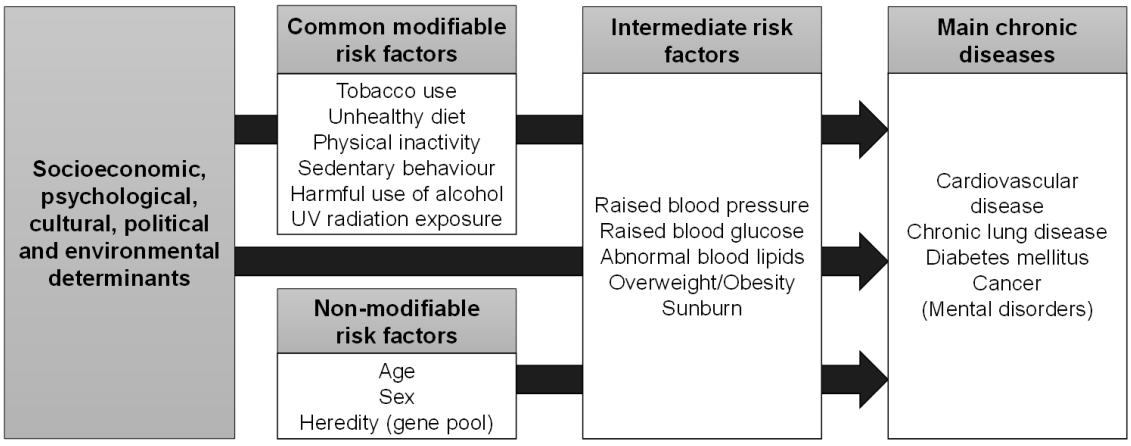
M: Males; F: Females

Source: (Ferlay et al., 2013; OECD, 2012d; WHO, 2012a)

Focus on risk factors

CNCDs are largely preventable through identifying and tackling the main modifiable risk factors, being health behaviours of which the most important are tobacco use, unhealthy diet, physical inactivity, sedentary behaviour, the harmful use of alcohol (WHO, 2015a), as well as exposure to ultraviolet (UV) radiation (as a risk factor for skin cancer) (Figure 3). It is estimated that if these main modifiable risks factors would be eliminated, about 80% of heart disease, stroke and type 2 diabetes as well as 40% of cancer could be prevented (WHO, 2005a). These health-related risk factors can lead to CNCDs directly, or indirectly through intermediate risk factors such as raised blood pressure or blood glucose, abnormal blood lipids, obesity and sunburn. There are an increasing number of studies suggesting that these modifiable health behaviours are also risk factors for common mental disorders (Akbaraly et al., 2009; Jacka, Mykletun, & Berk, 2012; Lucas et al., 2011; O'Neil et al., 2015; Pasco et al., 2008), although more research is necessary on the causality of health behaviours and mental disorders. In Figure 3 it is shown that the causes of CNCDs extend beyond the modifiable individual health behaviours and also include non-modifiable factors such as age, sex and the gene pool. Although there is agreement on inherited genes being a determinant of CNCDs, there is not yet a clear understanding to what extent the inherited gene pool plays a role in the onset of CNCDs (Billings & Florez, 2010; Cancer Research UK, 2015; Maes, Neale, & Eaves, 1997; WHO, 2016a). Additionally, there are external factors such as socio-economic (e.g. education, income), psychological (trauma, stress), cultural (religion), political (e.g. food taxes, price of natural resources such as sugar) and environmental characteristics (e.g. availability of walking trails), influencing the health of people (Magnusson, 2010). These external factors create the context in which people take health decisions, supporting or impeding healthy behaviour in the population. The impact of these different main risk factors makes prevention of CNCDs a complex task.

Figure 3: Main risk factors of chronic non-communicable diseases



Based on WHO report (World Health Organization, 2005b)

In order to explore the current prevalence of the major modifiable health risk factors for CNCDs, Table 2 presents the Belgian as well as the European prevalence of these risk factors (Eurobarometer, 2014; Eurostat, 2008b). Although the prevalence of overweight/obesity, smoking and vegetable consumption does not seem to be worse in Belgium compared to the European average, improvement is necessary. Besides, the prevalence of fruit consumption, alcohol consumption, physical activity and sedentary behaviour is shown to be worse in Belgium compared to the European average. According to the Belgian 'voedselconsumptiepeiling' 2014-2015, children between 3 and 5 years already spend half of the day sitting (average of 6.5 hours a day) and this increases with age, reaching a peak in adolescence (De Ridder, 2016). From the same survey, the average fruit consumption was shown to have decreased compared to 2004 and is still below the norm of 250-375 grams per day (De Ridder, Lebacq, Ost, Teppers, & Brocatus, 2016). Globally, improvement of risk factors for CNCDs is necessary in order to manage the rise in CNCDs.

Table 2: Prevalence of risk factors for chronic diseases in Belgium and Europe (2008)

	Overweight/ obese	Eating fruit ≤ once a week	Eating vegetables ≤ once a week	Walking ≥10 min/day for ≤3 days per week	Sitting ≥8h30 on a usual day	Smoking ≥ once a day	Drinking alcohol daily*
Belgium	47.5%	**8.3%**	1.0%	**57.0%**	**12.0%**	35.7%	**12.3%**
EU average	52.4%	**6.2%**	3.8%	**39.0%**	**11.0%**	37.3%	**6.8%**

** portion not specified*

Prevalence of risk factors being worse in Belgium compared to the European average are shown in bold

Source: (Eurobarometer, 2014; Eurostat, 2008b)

Early detection

Although the incidence of cancer might be reduced by identifying and modifying the main modifiable behaviours, these strategies cannot eliminate the majority of yet prevalent and irreversible but undetected cancers which are sometimes only diagnosed in late stages. Therefore, early detection, i.e. detection of a pre-cancerous or a cancerous lesion prior to the appearance of symptoms, could prevent disease progression and the associated health and economic consequences and thus is also a

cornerstone of cancer control (WHO, 2007). Early detection consists of two aspects, namely education to promote early diagnosis and screening. Information among health care providers and the general public is necessary to increase awareness and recognition of possible symptoms. Additionally, healthy individuals can be screened, using simple tests, in order to identify those who have the disease, but do not yet have clinical symptoms. Screening can consist of two strategies, namely screening based on symptoms or population-based screening of asymptomatic individuals to detect (pre-)cancerous lesions and to refer for diagnosis and treatment (WHO, 2007). Population-based screening programs can be organised for diseases eligible for screening according to the criteria of Wilson & Jungner (1968), such as when an effective test is available which is acceptable for the population, when the prevalence of the disease is high enough to justify the effort and costs of screening, when the natural progression of the condition is well understood and when facilities for diagnosis, treatment and follow-up are available.

1.2.3. Prevention on the policy agenda

Investing in prevention

Despite the reported burden of CNCDs, and the need for public health prevention programs, current health expenditure reveals that prevention is low priority for policy makers. Health systems are mainly focused on the (fragmented) care for the ill (Annemans, 2014). In Belgium, this is reflected in the average public expenditure on public health prevention programs being only 2% of the health budget, whereas the European average is 3% (OECD, 2012c). It would take about an extra €370 million per year of the Belgian health budget (Federale Overheidsdienst Budget en Beheerscontrole, 2016; Vlaamse Overheid, 2016) to be spent on prevention in order to reach the average expenditure on prevention in Europe. This care-oriented focus may relieve short term pressures, but failing to invest in prevention will increase the cost for treatment services in the long run. A lack of public investment in prevention has multiple reasons. One of the major reasons is the nature of the benefits of prevention, which mostly only occur on the long term, whereas people, and especially policy makers (because of their legislative term), have an inherent preference for short term benefits. Prevention of CNCDs leads to immediate costs and delayed benefits. Moreover, successful prevention is largely invisible, as it is difficult to measure how many cases of a disease have been prevented. Secondly, there is a lack of research providing the (health) economic information on prevention interventions. The U.K. Clinical Research Collaboration analysed the distribution of the budgets across eight major health-related research activity groups and found that only 5% of the funding is spent on prevention research (2015). However, several (recent) reviews (see paragraph 1.4.4. Cost-effectiveness of public health interventions) have shown a rise in the number of health economic evaluations of prevention programs in the past years. Another issue is that those who benefit from and those who bear the costs of prevention services are not always the same. This distortion emerges at the different policy levels but also between policy sectors. The current division of mandates in Belgium curbs an integrated and coordinated prevention policy. In Belgium, prevention is under the jurisdiction of the communities, while curative health care is regulated at the Federal level. This means that the costs of prevention and the benefits for the health care budget, due to increased population health, are situated on another legislative level. However, agreements between the different legislative

levels can be made, such as the co-financing of prevention programs. In case of the cancer screening programs in Flanders, the Flemish community and the Federal government have agreed that the Flemish community finances the organisation of the program (incl. the screening tests) and that costs of medical services related to and resulting from the program are funded by the Federal government (Federale Overheid, 2016). Lastly, budgets and interests are often in conflict with each other (Van Herck & Staelraeve, 2016). To what extent do schools for example need to invest financial resources in health promotion for children, in addition to their core education business, if the budget does not allow such convergence? There is a natural resistance to collaboration between policy departments, caused by a 'silo mentality'[5]. It is clear from previous points that the political structure of a country can affect the priority of prevention on the policy agenda.

Health in all policies

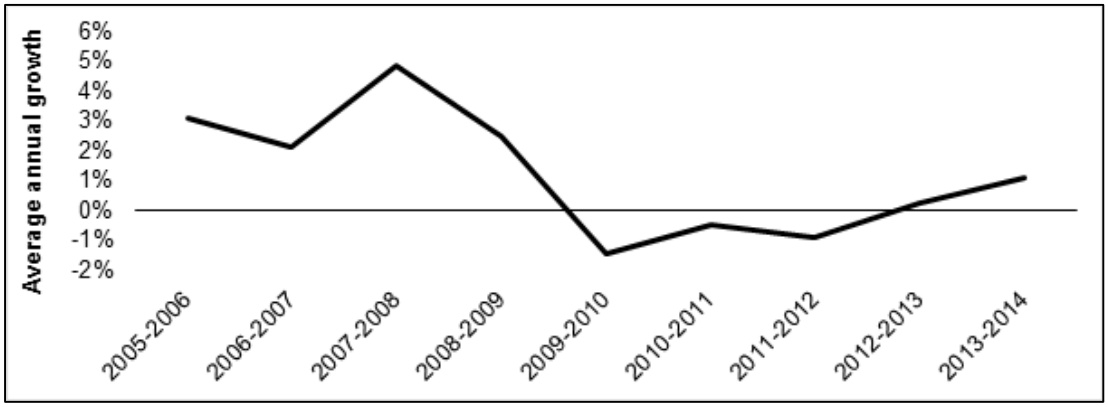
As shown in Figure 3, health is not only determined by health-related factors, but also by elements outside the health care sector. An effective health policy should involve all relevant policy areas at all government levels (European Commission, 2016). Health in All Policies (HiAP) is an approach that integrates health considerations at all levels of policy-making to improve the health of all communities and people (Leppo, Ollila, Pena, Wismar, & Cook, 2013). HiAP acknowledges that health is created by a multitude of factors beyond health care and, in many cases, beyond the scope of traditional public health activities. The HiAP-approach can be interpreted horizontally as well as vertically: on the one hand it implies that European, national, regional and local governments collaborate to take care of citizens' health; on the other hand it implies including health considerations in policy making across different sectors that influence health, such as mobility, housing, education, employment, taxation, etc. Some HiAP-examples are: fall prevention by modifying the physical environment in residential care centres, or by giving an information session organised by the municipality; creation of parks and play forests in the city or town to improve sedentary behaviour, physical activity and increase mental wellbeing; financially rewarding schools or employers who are committed to improve the health of their students or employees; actions such as 'met belgerinkel naar de winkel' (organised by 'Bond Beter Leefmilieu Vlaanderen') in which every Flemish community can participate in order to promote shopping by bike instead of car; European legislation on health, implemented at national level, such as the guidelines for the quality of the screening program for breast cancer, food labelling , ...

[5] A silo mentality is a mindset occurring when departments do not share information, goals, tools, priorities and processes with other departments. The silo mentality may contribute to a decreased performance and has a negative impact on the corporate culture.

1.3. Health budgets under pressure

In 2013, public health expenditure[6] (PHE) in Europe consisted of 6.5% of the gross domestic product (GDP) (OECD, 2015b). In Belgium the current public health care budget (i.e. at the Federal and community level, anno 2016) amounts to about €37 billion, which is 9% of the GDP. Since 2000, the PHE in Belgium, as a share of the GDP, has increased from 5.9% to 9%. This trend has mainly been nourished by a rise in the incidence of CNCDs as a consequence of changing health behaviour and population ageing -but also by technological progress, rising patient expectations and inefficient use of the health budget (Pammolli, Riccaboni, & Magazzini, 2012; WHO, 2015b). As such, the concern has been raised on the financial sustainability of the health care system. In the wake of the financial and economic crisis however, from 2009 on, health spending growth slowed down, in some countries even to negative growth figures (Figure 4). The crisis had a large negative impact on the availability of health system resources (Mladovsky et al., 2012), and as a response, several countries reported cuts in the national health budget, resulting in a slow-down or even fall in the health spending growth rate (Mladovsky et al., 2012; OECD, 2012b).

Figure 4: Average annual growth in per capita public health spending in Europe, 2005-2014



(OECD, 2015b)

The OECD reported the largest health budget cuts in 2009-2010 to be made in the sector of public health and prevention and of pharmaceuticals (McDaid et al., 2013; OECD, 2012c). Since 2010, PHE is slightly increasing again, and in recent years, increases in health spending are in line with overall economic growth (at a rate of about 1%), so that the health expenditure as a share of GDP remains stable (OECD, 2015a). However, as a response to cuts in the health budget, the European Commission published a report on “Investing in Health”, in order to inform and convince every country to invest in health (2013). Increases in health spending produce significant increases in health, particularly for increases in spending in prevention (Vavken, Pagenstert, Grimm, & Dorotka, 2012). Moreover, people

[6] Public health expenditure consists of spending from government (central and local) budgets, external borrowings and grants (including donations from international agencies and nongovernmental organisations), and social or compulsory health insurance funds (The World Bank, 2016). Specific for the Belgian case PHE includes all direct health care spending by social security institutions, the federal government, the regions and communities, and local governments, including spending on disease prevention.

with better health are capable of producing more goods and services than those in poor health, leading to faster economic growth (European Commission, 2010b). An additional response to the difficulties in sustaining the health system came from the Institute for Health care Improvement, who developed a framework to address the objectives that should be pursued by the health care system, called the Triple Aim (2016). The Triple Aim stands for improving the health of populations, improving the patient experience of care (including quality and satisfaction) and reducing the per capita cost of health care. Indeed, the health care system should improve health within the limited budget, taking into account the quality of care. The policy emphasis should be on spending the money wisely (i.e. more efficiently), eliminating wasteful spending, encouraging personal responsibility for health and investing in prevention (Mladovsky et al., 2012; Moodie, 2013; Wanless, 2004). Consequently, policy makers need to make choices, towards the most efficient interventions and strategies (Drummond et al., 2015). Getting more value for money is crucial if countries are to ensure population health, under conditions of severe constraints on public budgets (Council of the European Union, 2010).

1.4. Health economic evaluations

In light of the pressure on health expenditure and budget constraints, policy makers have to make decisions on what interventions to offer and how the interventions should be provided in order to achieve an optimal health gain with available resources. This means that beside evidence on the efficacy and effectiveness[7] of a health intervention, also information on the efficiency is necessary. Efficiency or cost-effectiveness addresses the question whether it is worth implementing an intervention, compared to other interventions that could be implemented with the same budget (Annemans, 2008). Health economic evaluations are a valuable tool in the decision making process by informing on the efficiency of alternative health interventions and strategies, in terms of the incremental costs and health benefits of one intervention compared to another intervention or to the current standard (which can be no intervention). A health economic evaluation is defined as “the comparative analysis of alternative courses of action in terms of both their costs and consequences” (Drummond et al., 2015).

1.4.1. Types of health economic evaluations

Four general types of health economic evaluations exist: cost-minimisation analysis, cost-benefit analysis, cost-effectiveness analysis and cost-utility analysis. All four methods measure costs in the same way; the distinguishing feature of each is the way in which benefits are measured. Table 3 summarises the characteristics of the four different types. Cost-minimisation analysis assumes -based on available evidence- the health effects of the alternatives to be equal, and therefore only considers the costs related to the analysed interventions (Drummond et al., 2015). In this way, the least costly intervention is the most efficient. Cost-benefit analysis measures costs as well as health benefits in monetary units. The outcome, expressed as net monetary gain/loss or as a ratio of benefits and costs,

[7] Efficacy is achieved when the strategy leads to the intended health benefits in a controlled setting
Effectiveness is achieved when the strategy leads to the intended health benefits in real-life (Annemans, 2008)

can be compared between different alternative interventions. Cost-benefit analyses are not frequently performed, since the main challenge is valuing the benefits –such as deaths or disease prevented- in monetary units. Cost-effectiveness analysis compares interventions with the same objective. It measures the benefits of an intervention in natural units associated with the primary outcome (e.g., cases prevented, deaths prevented, life-years gained, decrease in BMI-units) and the costs in monetary units. The most common health economic evaluations are cost-utility analyses, which are a type of cost-effectiveness evaluations and therefore usually called as such. Cost-utility analysis compares interventions with different objectives (i.e. across different pathologies). Guidelines on performing health economic evaluations usually advise to express health benefits as a generic measure such as disability-adjusted life-years (DALYs) or quality-adjusted life-years (QALYs) (Cleemput, Neyt, Van de Sande, & Thiry, 2012). QALYs are more commonly used as generic outcome measure in reference to DALYs. QALYs are measured by utility weights which have a value between 0 (death) and 1 (perfect health). Belgian guidelines recommend to derive these utilities indirectly by specific pre-scored generic patient questionnaires. The most common and recommended questionnaire is the EuroQol Quality-of-Life instrument (EQ-5D) including five dimensions, namely mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and three or five answer levels (from no problems to severe problems/unable) (EuroQol, 2016). The pre-scored EQ-5D value sets are elicited from the general population and are available for different countries. QALYs are calculated by multiplying the utility weight with the number of life years spent in a particular disease state. As such one QALY is equal to one year in optimal health. In this PhD-thesis, all included health economic evaluations were cost-effectiveness analysis, more specifically cost-utility analyses, expressing the health benefits in QALYs gained. Costs were included from a health care- as well as a societal perspective, encompassing medical costs as well as costs due to productivity loss.

Table 3: Characteristics of the different types of economic evaluation

Method	Costs measurements	Effect measurements	+ Advantages - Disadvantages
Cost-minimisation analysis	Incremental costs in monetary units	Health effects are not measured, since they are considered to be equal	+ Simple and easy to understand - Should not be interpreted as a full economic evaluation
Cost-benefit analysis	Incremental costs in monetary units	Incremental health effects in monetary units	+ Allows comparison of interventions across the entire economy - Difficult to place a monetary value on health outcomes*
Cost-effectiveness analysis	Incremental costs in monetary units	Incremental health effects in natural units (BMI-points lost, burns prevented, etc.)	+ Easy to interpret and to communicate - Does not allow to compare interventions across different pathologies
Cost-utility analysis	Incremental costs in monetary units	Incremental health effects in generic outcomes such as QALYs or DALYs	+ Allows comparison of interventions across different pathologies - Generic outcome measure such as QALY may not capture all intervention outcomes such as those external to the health sector

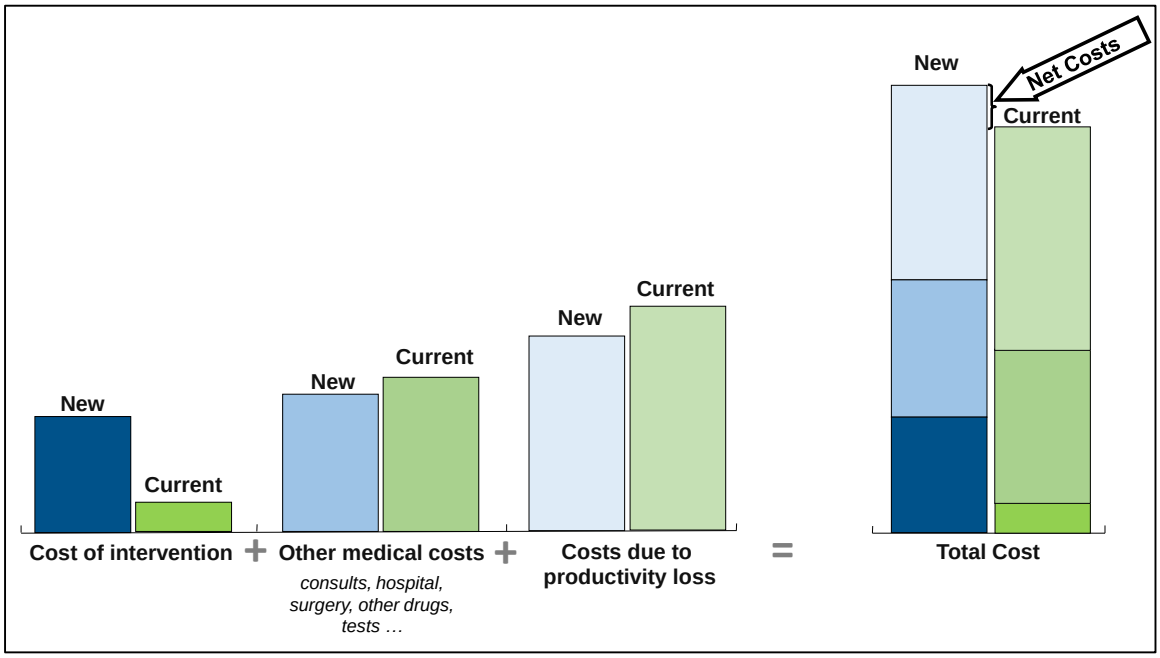
*In the health sector, market prices are often lacking. Surveys can be used to estimate hypothetical willingness-to-pay.

QALYs: Quality-Adjusted Life-Years; DALYs: Disability-Adjusted Life-Years. Source: (Drummond et al., 2015).

1.4.2. Incremental cost-effectiveness ratio

The outcome of a cost-effectiveness analysis is calculated as the difference in costs between the evaluated intervention and the comparator, divided by the difference in health benefits, called the incremental cost-effectiveness ratio (ICER). The ICER is expressed as a cost per unit of health benefit gained. A new intervention usually induces an extra intervention cost, and can lead to extra costs or cost-savings in the medical costs and costs due to productivity loss (Figure 5). Depending on the size of the costs in these cost categories, the new intervention will induce an extra total cost in reference to the comparator, or lead to total cost savings. Figure 5 shows the example of an intervention leading to a total net cost.

Figure 5: Visualisation of the incremental costs related to a new compared to a current health intervention

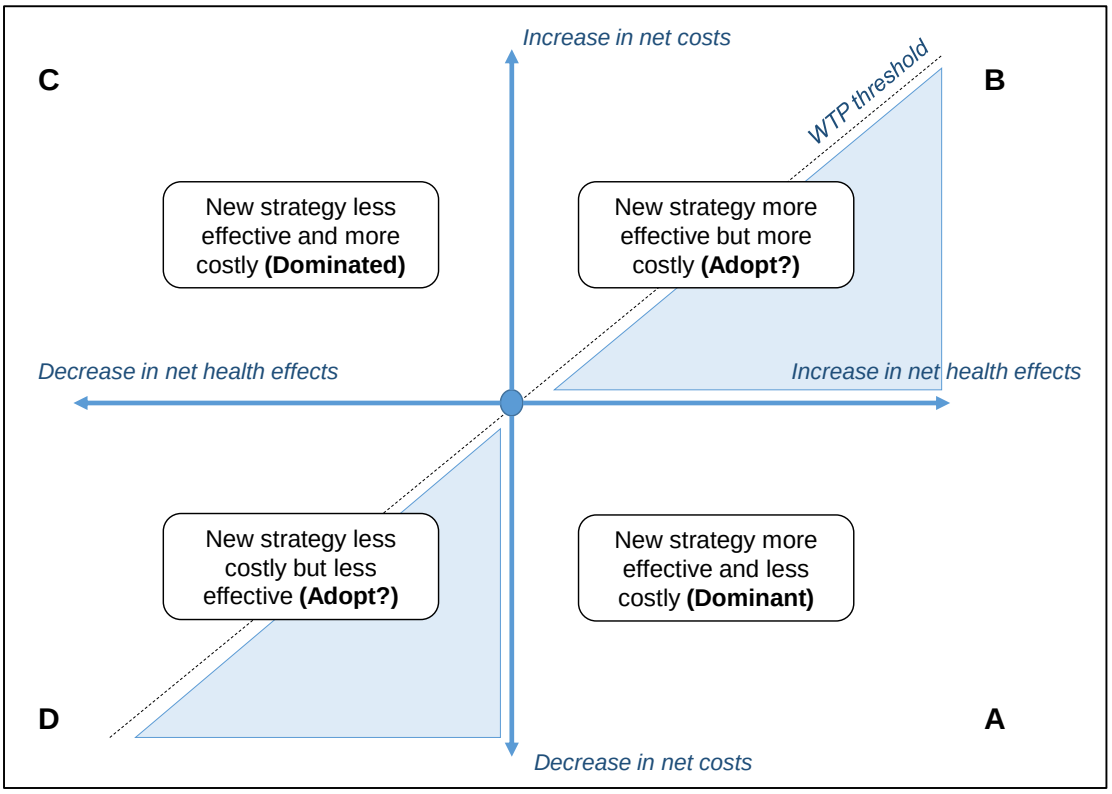


Even in the case of an extra total cost, the new intervention can be cost-effective compared to the comparator arm. Figure 6 shows the quadrants of the cost-effectiveness plane, representing the combinations of possible outcomes of incremental costs and health effects. Interventions situated in quadrant A and C are easy to evaluate. If a new intervention induces less total costs than the comparator intervention and generates greater health benefits, then this new intervention is called dominant and thus obviously cost-effective (quadrant A) (Briggs, Sculpher, & Claxton, 2006). Interventions in quadrant C are not desirable as they cost more but do not lead to extra health benefit and will therefore be excluded from the decision process. Decisions on interventions situated in quadrant B and D are more difficult to make. Interventions situated in quadrant D are not only decreasing the total cost but also the health benefits. If the cost-savings are large enough to compensate for the health loss, such interventions can be cost-effective[8]. If the net health benefits of interventions in quadrant B compensate

[8] Denoted with the term 'decrementally' cost-effective (Nelson, Cohen, Greenberg, & Kent, 2009). There is debate however on the threshold value in the south-west quadrant of the cost-effectiveness plane, namely whether or not it should be the same as in the north-east quadrant (Dowie, Kjer Kaltoft, Bo Nielsen, & Salkeld, 2015).

for the additional costs, then this new intervention can be cost-effective, depending on the societal willingness-to-pay threshold. If the ICER is below the threshold, the evaluated intervention is considered as cost-effective, i.e. offering good value for money (cf. the light blue surface in Figure 6). The lower the ICER, the better the cost-effectiveness. If the ICER is above the threshold, the intervention is not considered to be cost-effective and allocation of resources to this intervention is unlikely to increase efficiency.

Figure 6: Four quadrants of the cost-effectiveness plane



WTP:Willingness-To-Pay

Interventions situated in the light-blue surfaces should be interpreted as cost-effective, dependent on the WTP-threshold.

Some countries have an explicit threshold value or value range, such as the United Kingdom (£20,000 to £30,000) but most countries, including Belgium, do not. There are three common approaches to determine a threshold of which the most common one is the approach proposed by the WHO, namely based on the GDP per capita (WHO, 2005b). In this PhD-thesis, an intervention was considered to be cost-effective if the ICER was below the threshold of one time the Belgian GDP per capita, set at 35,000/QALY gained. However, this is a rather informal threshold and deviations, based on other criteria (see section 1.5.2.), are possible. Besides, by using a cost-effectiveness threshold based on the GDP per capita, it is assumed that the country is willing to pay up to that threshold for the health benefit, usually without any concrete evidence of that willingness to pay. Other approaches to determine the threshold are based on a benchmark intervention, by retrospective analysis of existing practice, or ranking interventions in a league table (Marseille, Larson, Kazi, Kahn, & Rosen, 2015). Considering a benchmark intervention to set the cost-effectiveness threshold has more local relevance than a threshold based on GDP. However, which benchmark intervention to choose is not straightforward; the

benchmark intervention may be a high or low outlier. It may for example have resulted from a political decision that does not reflect the current, true measure of societal willingness to pay for health benefits (Marseille et al., 2015). A league table lists all relevant health interventions based on their incremental cost-effectiveness ratio, with the best ratio on top and the worst ratio at the bottom of the ranking. The league table approach is based on the principle that health outcomes are maximised if selection of the options for implementation begins with the best ICERs, which are shown at the top of the league table and then moves down the list until the budget is exhausted. The disadvantage of a league table is that much information is needed on the cost-effectiveness of other interventions to prepare the table. However, this information is not always available.

1.4.3. Cost-effectiveness models

In order to predict long term costs and health effects associated with an intervention, most cost-effectiveness analyses make use of modelling techniques. The most frequently used models are focusing on the average patient and are called cohort models. The two most common examples of cohort models are the decision tree and the Markov model. A decision tree is the simplest of both modelling techniques, representing disease prognosis, following an intervention, by a series of (mutually exclusive) pathways (Briggs et al., 2006). It estimates the likelihood of various outcomes, according to a certain probability, and applies associated costs and benefits for each pathway. The decision tree is suited to diseases where events occur over a discrete short time period. This method is however of limited use for more complicated diseases, with lengthy prognosis, or for events that are likely to recur over time, such as in the case of chronic diseases. It can however be used as a submodel in a larger model, e.g. to identify the number of cases detected by a screening program. A Markov model simulates disease progression, allowing to address more challenging problems (Briggs et al., 2006; Sun & Faunce, 2008). This method is suited to model long term outcomes, where the timing of events is important and when events may happen more than once. Therefore, Markov models are particularly suited to evaluate chronic diseases (Briggs et al., 2006). A Markov model consists of a set of health states in which an individual can be at a certain point in time. The individual can only be in one health state at a time, and can transition to another state within a certain period, which is called the cycle length. The risk to move from one to another state is determined according to the transition probabilities, derived from clinical and epidemiological evidence. All individuals in a certain health state are assumed to have identical characteristics, meaning that the transition probabilities can only depend on the current health state and not on past health states (called the Markovian assumption). Each health state is assigned costs and health effects (usually defined as QALYs). The length of the time horizon (i.e. the time span for which costs and effects should be measured or estimated), should be sufficiently long to capture all relevant differences in costs or outcomes between the compared interventions. Many public health interventions result in immediate costs, but may also lead to future health benefits and/or cost-savings. Due to time preference (i.e. future costs and benefits are valued less than current costs and benefits, as in the mean time we can benefit from them), future costs and health benefits should be recalculated to their present value, which is called discounting (Drummond et al., 2015). According to the Belgian guidelines, a discount rate of 1.5% is applied to future health benefits, and 3% to future costs (Cleemput et al., 2012).

The ICER is then the ratio of the difference in the summed costs and QALYs between the evaluated interventions at the end of the time horizon.

1.4.4. Cost-effectiveness of public health interventions

In the past 5 to 10 years, an increasing number of reviews on the availability of cost-effectiveness analyses of prevention interventions have been undertaken. Cohen et al. (2008) and Neumann et al. (2015) found that only 19%-35% of all analysed cost-effectiveness ratios were classified as preventive, while 65%-81% pertained to treatments. Additionally, Schwappach et al. (2007) showed in their review on the economic evidence of primary prevention of cardiovascular disease that 83% of the studies they retrieved analysed individual clinical prevention interventions (surgery, pharmacotherapy) and only a minority of the studies were about health promotion addressing a community of people (10%) and about screening (3%). Winn et al. (2016) found that the proportion of studies focusing on prevention of cancer has increased from an average of 4 studies per year between 1998 and 2006 to 21 studies per year between 2007 and 2011 and 24 studies per year in 2012 and 2013. Most of the studies they analysed were however focusing on individual-oriented treatment strategies (chemotherapy and post-diagnosis interventions), accounting for 71% of the evaluated strategies. Despite the more numerous economic evidence on treatments (drugs and medical technologies), there is evidence of increasing interest in analysing the cost-effectiveness of public health interventions in the last decade (Cobiac, Vos, & Veerman, 2010; Rush, Shiell, & Hawe, 2004; Schwappach, Boluarte, & Suhrcke, 2007; Winn, Ekwueme, Guy, Jr., & Neumann, 2016).

The health benefits of prevention are intuitive, and policymakers and professionals often believe that prevention always saves money (Woolf et al., 2009). However, it is impossible to generalise about prevention interventions as if their results were all alike. In particular, the evidence does not support the commonly accepted idea that prevention always, or even usually, reduces medical costs -although it sometimes does (Cohen, Stolk, & Niezen, 2008; Goodell, Cohen, & Neumann, 2009; Russell, 2009; Russell, 2007). Moreover, as stated before, the question is not whether an intervention saves money, but whether it offers good value for money. Investing in cost-effective prevention strategies could increase the years lived in health while helping to control the growth in health care expenditure (European Commission, 2010b). Although Cohen et al. (2008) found that preventive interventions are not necessarily more cost-effective than treatment strategies, some promising results were found in other review studies. Owen et al. (2012) reviewed 200 cost-effectiveness estimates from 21 studies published between 2006 and 2010 (especially concerning smoking and physical activity) and found that the majority of studies (70.5%) had a cost-saving or very cost-effective result. Van Gils et al. (2011) confirmed this conclusion. Cobiac et al. (2010) evaluated the cost-effectiveness of 23 nutrition interventions and found that 72% of the reviewed interventions were cost-saving or cost-effective, especially interventions targeting the whole population (such as changing policies) rather than high-risk individuals. Chokshi & Farley (2012) showed that environmental interventions (i.e. interventions that act on persons indirectly by altering the physical or social environment, such as transfat bans) seem to be more cost-effective than clinical interventions (such as cancer screening) or non-clinical, person-directed interventions (such as a suicide prevention helpline). Sassi et al. (2009) analysed the cost-

effectiveness of 42 primary prevention programs, including food labelling, food advertising regulation, physician-dietician counselling, mass media campaigns, worksite interventions, school-based interventions, fiscal measures and food advertising self-regulation. They found that most interventions were cost-effective, with the two latter intervention strategies generating cost-savings. Although publication bias (i.e. overrepresentation of positive results in the literature) can play a role in these results, they seem to be promising.

1.4.5. Uncertainty in cost-effectiveness analysis

It is important to note that despite the value and the relevance of cost-effectiveness analyses, they include inherent uncertainties (Annemans, 2008). There are different sources of uncertainty, related to the structure of the model (structural uncertainty), uncertainty associated with parameters (parameter uncertainty), or uncertainty due to the choice of methods (methodological uncertainty) (Briggs et al., 2006). Structural uncertainty refers to uncertainty about the extent to which a model adequately represents the health condition and intervention under evaluation. Parameter uncertainty is inherent in decision models as the true value of the input parameters is almost always unknown. Therefore, estimates of the true value are rather used and in case of lack of data assumptions have to be made. Additionally, several aspects of the underlying methods used in the particular cost-effectiveness analysis could be debated. Sources of methodological uncertainty are the perspective adopted in order to select the included costs (e.g. societal or health care payer perspective), (valuation of) health outcomes, duration of the intervention effect, length of time horizon, selection of discount rates and so on. (Bojke, Claxton, Sculpher, & Palmer, 2009). Jain et al. (2011) reviewed cost-effectiveness analyses published between 2000 and 2009 and found that almost 90% of the included articles addressed parameter uncertainty, while only 33% addressed methodological uncertainty and 8% addressed structural uncertainty.

It is important to present results of the cost-effectiveness analysis in a transparent way, while exploring the uncertainty in key parameters and pay attention to validating the model and the model outcomes (Simoens, 2009). In order to improve the quality of cost-effectiveness analyses, the guidelines state that uncertainty should be explored by running sensitivity- and scenario analyses (Eunethta, 2015). In the studies included in this PhD, parameter values were varied one by one in one-way sensitivity analyses, to test the impact on the incremental cost-effectiveness ratio. In this way, the parameters with the greatest effect on the ICER as well as the magnitude of their effect can be determined. Another type of sensitivity analysis that was used to quantify uncertainty is probabilistic sensitivity analysis. This type of sensitivity analysis varies the values of all relevant parameters together, according to their probability distribution. Samples from these distributions are randomly drawn and generate a confidence interval around the ICER. Additionally, from a probabilistic sensitivity analysis a cost-effectiveness acceptability curve (CEAC) was drawn, to indicate the probability of the result being cost-effective considering a specific willingness-to-pay threshold. In a scenario-analysis, several methodological as well as structural assumptions were evaluated. In the review of Jain et al. (2011), 86% of the included articles conducted a one-way sensitivity analysis and 45% a probabilistic sensitivity analysis or a scenario-analysis. The use of CEACs increased over time from 3% in 2000-2003 to 36% from 2006 to mid-2009.

In addition to sensitivity- and scenario analyses, the validity of the model structure, input parameters, methodological assumptions as well as the outcomes of the studies included in this PhD, was assessed as much as possible by model validation. According to a report of the International Society for Pharmaco-economics and Outcomes Research's Task Force for Modeling Good Research Practice, model credibility can be enhanced by means of transparency and validation (Eddy et al., 2012; Husereau et al., 2013). Transparency is about clearly describing the model structure, calculations, parameters values and assumptions so that interested parties are able to understand the model and the results. Validation has been defined as the set of methods for judging a model's accuracy in making relevant predictions (Eddy et al., 2012; Gray, Clarke, Wolstenholme, & Woodsworth, 2007). There are several types of validation: face validation, internal validation, cross-validation, outcome validation and predictive validation. *Face validity* represents the extent to which the model design corresponds to current (medical) evidence, as judged by experts. *Internal validity* addresses whether the model has been implemented correctly. *Cross-validation* implicates comparing the results of a model with other studies addressing the same research question to determine the extent to which they calculate similar results. *Outcome validation* consists of testing the outcomes of the comparator (which usually represents the current standard) with observed parameters. *Predictive validation* concerns the comparison of the predicted outcomes by the intervention arm with the outcomes observed in real-life. It refers to the ability of the model to make accurate predictions of future events. Despite the importance of validation in cost-effectiveness analysis, and although validation is deemed important by many researchers, it is often omitted in the reporting of health economic modelling studies (de Boer, Frederix, Feenstra, & Vemer, 2016; Koleva-Kolarova, Zhan, Greuter, Feenstra, & de Bock, 2015). Furthermore, there is no measure to decide how valid a model is. For example, the question of how close predictions of a model must be to observed data in real-life in order to be considered valid is impossible to answer (Eddy et al., 2012), although this should not affect the importance of model validation. The degree of accuracy also depends on the question that needs to be informed. For example, much less accuracy is needed to inform "Will this intervention increase or decrease costs?" than to answer "How much will this intervention cost?" (Eddy et al., 2012). The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist has been developed to optimise reporting of health economic evaluations, but unfortunately no clear guidelines for the reporting of validation exercises are included in this checklist (Husereau et al., 2013). We will further elaborate on this topic in the general discussion of this PhD.

1.5. Cost-effectiveness in policy

1.5.1. Cost-effectiveness evidence informing policy

Health economic evaluations cannot aid in the optimal use of the health budget unless research translates into policy. In the domain of health, the principles of evidence-based medicine are slowly spreading in the context of policy making. Nevertheless, the use of economic evidence has gained less importance than evidence on clinical effectiveness (Corbacho & Pinto-Prades, 2012; Eddama & Coast, 2008; Merlo, Page, Ratcliffe, Halton, & Graves, 2015). In Belgium, the process for reimbursement of drugs is quite structured. The request for reimbursement is assessed by the Commission for Drug

Reimbursement. The evaluation is based on some key criteria (defined by law) including the cost-effectiveness (next to added therapeutic value, the proposed price and reimbursement level, the medical need and the budget impact) (Federale overheidsdienst sociale zekerheid, 2001). However, decisions on public health interventions are much less structured and it is not clear to what extent cost-effectiveness is used as a criterion. In Flanders though, prevention interventions seem to be increasingly tested for their cost-effectiveness (Van Herck & Staelraeve, 2016). Nonetheless, the systematic review of Eddama et al. (2008) describes an overall limited use of cost-effectiveness analysis in local decision-making. Several studies explored the most important barriers for policy makers to make use of economic evidence in their decisions (Eddama & Coast, 2008; Eddama & Coast, 2009; Galani & Rutten, 2008; Merlo et al., 2015; Niessen et al., 2012; Oliver, Innvar, Lorenc, Woodman, & Thomas, 2014; Williams & Bryan, 2007). The main factors were described as the availability of relevant research in a timely manner (timing), the objective as well as perceived quality and transparency of the evidence, the clarity of its presentation, the extent to which it can be understood by the policy makers and the short term focus of policy makers. Policy makers often struggle to understand health economic analyses, mainly because of the language and concepts used in such analyses, and the presentational styles adopted. Moreover, commissioning cost-effectiveness research that can be delivered in a timely manner necessitates funding, which often is a barrier for policy makers. The review of Merlo et al. (2015) summarised some solutions to these barriers that were suggested in several studies: more cooperation between researchers and policy makers could positively influence the impact of economic evaluations on policy, training for policy makers could allow them to better interpret the design and results of economic evaluations and standardised formats for presenting the results of economic evaluations.

1.5.2. Other important criteria in the decision making process

Despite the value of cost-effectiveness evidence in the decision making process, it must be noted that cost-effectiveness is and should not be the only criterion for decision making. Multiple factors impact the decisions of policy makers (Thokala et al., 2016; Weintraub & Cohen, 2009), although the weight of these different factors is not transparent. Cost-effectiveness estimates should be used as a decision aid, not a decision rule (McDaid, Drummond, & Suhrcke, 2008). Only taking into account the cost-effectiveness of an intervention or strategy might conflict with other policy goals. A recent systematic review on priority setting with explicit criteria to guide decision-making found that the following criteria emerged as being most common: effectiveness, cost-effectiveness, budget impact, medical need and equity (Cromwell, Peacock, & Mitton, 2015). This wider context is the focus of Health Technology Assessment (HTA), which is “the systematic evaluation of the properties and effects of a health technology[9], addressing the direct and intended effects of this technology, as well as its indirect and unintended consequences, and aimed mainly at informing decision making regarding health technologies. HTA is conducted by interdisciplinary groups that use explicit analytical frameworks

[9] A health technology is defined as an intervention that may be used to promote health, to prevent, diagnose or treat acute or chronic disease, or for rehabilitation. Health technologies include pharmaceuticals, devices, procedures and organisational systems used in health care (International Network of Agencies for Health Technology Assessment, 2016).

drawing on a variety of methods" (International Network of Agencies for Health Technology Assessment, 2016).

Beside *effectiveness* and *cost-effectiveness* another important consideration when establishing priorities in the public sector is the *budget impact* of an intervention, denoting the impact of a positive policy decision on the health care budget. A cost-effectiveness analysis informs about the comparative value for money an intervention offers, whereas a budget impact analysis helps to determine whether the health care payer can afford to implement a particular intervention (Cleemput et al., 2012), as it takes into account the total population to which the intervention would apply. A budget impact analysis is especially useful in the case of universal prevention, because of the large extent of the target population receiving the intervention. However, there is no clear reference as to what an acceptable budget impact is. This decision has to be made by the health care payer. In case the budget impact analysis estimates total cost savings by means of the intervention, a return on investment can be calculated, measuring the benefit for the payer resulting from the original intervention investment. The *medical need* of a new intervention is shaped by the morbidity and mortality caused by the health problem. Burden of disease studies can inform researchers and policy makers on the medical need. Burden of disease studies include studies on the total health burden to an individual or society because of a disease and studies on the financial impact of a disease to an individual or society. The latter studies are often called cost-of-illness studies. Cost-of-illness studies calculate the total costs of a particular disease with the aim of giving an idea of its economic burden. By measuring the health- and economic burden of a specific disease, such burden of disease studies can help health care decision makers to set up and prioritise health policies and interventions. According to Stolk et al. (2005) applying medical need as decision criterion means that "the relative efficiency criterion should be applied differently when the disease problem is more or less disabling, by varying the cost-effectiveness threshold in reimbursement decisions according to burden of disease". Beside medical need, costs and benefits, another criterion likely to be of concern is the distribution of those benefits, reflecting *equity issues*. Questions related to this equity concern are: do all individuals with equal need have the same access to the intervention?, Does the intervention particularly benefit those with severe health conditions?, does the intervention particularly benefit the poor? (James, Carrin, Savedoff, & Hanvoravongchai, 2005).

To conclude, it is possible that a prevention intervention, which has been shown to offer good value for money, does not receive public funding because it does not meet one or more of the above mentioned criteria. David Haslam, the chairman of the National Institute for Health and Care Excellence (NICE) stated it as follows: "One of the critical roles of the NICE committees I have tried to ensure is for them to use their judgement, not just to follow simple algorithms. If we had simple algorithms that could do this, we could replace everyone with a computer, but that's not the point: we're here to make complex judgements on behalf of society" (Pharmafile, 2014). In the United Kingdom a Value-Based approach was introduced, in order to create flexibility in the decision making (National Institute for Health and Care Excellence, 2014). If for example, a new technology increases the quality and length of life at the end of life, a higher willingness-to-pay threshold may be assumed. As such, the assumed threshold in cost-effectiveness analyses is not rigid and the ICER should be interpreted as an extra source of information to the normative decision process. Of course, this list of abovementioned criteria in the decision-making

process is not exhaustive, and many other factors can influence policy decisions such as contextual factors (stakeholder interests and pressures), quality and strength of the evidence and complexity of the intervention (organisational requirements and capacity to implement) (Guindo et al., 2012). For example, sometimes it might be the case that a public health intervention is introduced before any strong evidence of (cost-)effectiveness is available, if leader opinion is strong or if there is pressure to focus on the 'hot topics' in health (Curtis, 2012; Specchia et al., 2015). However, this is not an argument against the use of cost-effectiveness evidence in health care decision making. A decision only based on cost-effectiveness considerations is a wrong decision, but neglecting cost-effectiveness information in the decision making process is unethical.

1.5.3. Transferability of cost-effectiveness results

Information on the cost-effectiveness of a particular health technology is not always available on the short term, which might be a barrier for policy makers to inform their decision by cost-effectiveness evidence. Sometimes however, similar studies on the cost-effectiveness of the particular health technology in other countries might be transferable to the own context. Transferability refers to "the extent to which the results of a study, as they apply to a particular patient population and/or a specific context, hold true for another population and/or in a different context" (Briggs et al., 2006). The issue of transferability of cost-effectiveness studies from one country to another gains increasing interest, particularly in times of budget or time constraints. There are several reasons why cost-effectiveness results of similar interventions might differ between countries, such as demography and epidemiology of the condition, clinical practice, costs for treatment of a condition, etc. Consequently, health economic evidence cannot be considered to be always directly transferable between settings (Drummond et al., 2009), although it might be possible taking certain aspects of the particular study into account.

According to the model of Welte (2004), a study is not transferable if the relevant technology is not comparable to the one that will be used in the decision country; if the comparator is not comparable to the one that is relevant to the decision country or if the study does not possess an acceptable quality. In case these criteria are not met, the study might be transferable. In order to determine the level of transferability, the level of correspondence between the study country and the decision country on several transferability factors is to be estimated (Table 4). Finally, the likely effect of the factor on the cost-effectiveness result should be determined. When both the relevance of the factor and the correspondence between the countries is high, the transfer of the study result will be unbiased. After these three steps, it can be decided which adjustments are necessary to transfer the foreign studies.

Table 4: Specific transferability criteria of Welte's model

Transferability characteristic	*Transferability factor*
Methodological characteristics	perspective; discount rate; medical cost approach; productivity cost approach
Health care characteristics	absolute and relative prices; practice variation; technology availability
Population characteristics	incidence/prevalence; life expectancy; health-status preference; acceptance, compliance and incentives to patients; productivity and work-loss time; disease spread

Source: (Welte, Feenstra, Jager, & Leidl, 2004)

1.6. Aims and outline of this study

Action is necessary in order to control the burden of CNCDs on public health as well as on the public health care expenditure. Evidence on effectiveness and cost-effectiveness of prevention programs provides policy makers with information in order to make priorities and spend the budget wisely. Cost-effectiveness analyses of public health interventions are increasingly performed, although not yet reaching the same levels as clinical individual-based interventions, such as drugs, devices and medical procedures. Nonetheless, cost-effectiveness analyses do have potential for public health interventions too. The main question that precedes a cost-effectiveness analysis of public health interventions is the same as for health care interventions, namely whether the intervention offers value for money. However, the use of cost-effectiveness evidence, especially of public health prevention interventions, has been estimated to be limited. This is mainly due to the availability, quality and transparency of such evidence, the clarity of its presentation and the extent to which policy makers understand such analysis. Therefore, the first aim of this thesis was to assess the cost-effectiveness of 8 public health interventions in the continuum of prevention, that hold some promise to reduce the health burden at a reasonable or lower total cost. However, cost-effectiveness analyses of public health interventions involve some uncertainties, mainly due to the particularities of the field (Weatherly et al., 2009). Uncertainty in the public health intervention analyses should be acknowledged, e.g. concerning the future benefits (how long does the effect maintain), attribution of long-term effects based on intermediate effects, use of QALY as outcome measure …The second aim was to inform researchers, health professionals as well as policy makers on the interpretation of cost-effectiveness results in light of uncertainty and the use of such information by reporting and reflecting on the main uncertainties that were encountered in the included cost-effectiveness analyses.

The first part of this PhD-thesis consisted of a general introduction outlining the research background. The second part represents the different health economic evaluations within each prevention category. Each of the case studies are based on a paper which has been published or submitted for publication in a peer-reviewed journal. The first evaluated intervention is categorised as **universal prevention** and concerns the obesity problem. It is estimated that more than half (52%) of the adult population in the European Union are overweight or obese (OECD, 2012a). Additionally, around 1 in 3 European children aged 6-9 years old are overweight or obese (Wijnhoven et al., 2014). Childhood obesity is associated with a higher chance of obesity, premature death and disability in adulthood, especially due to cardiovascular disease, diabetes, and cancer (Acosta, Manubay, & Levin, 2008; Baker, Olsen, & Sorensen, 2007; Venn et al., 2007). *The ToyBox intervention* is a kindergarten-based, family-involved intervention to prevent obesity in early childhood (3.5 to 5.5 year-olds). It was implemented throughout 2012-2013 in Belgium, Bulgaria, Germany, Greece, Poland and Spain. The intervention focused on four key health behaviours being physical activity, sedentary behaviour, snacking behaviour and drinking behaviour. As this intervention targeted the pre-schooler population, it could have been categorised as a selective prevention intervention as well. However, as almost all children between 3.5 and 5.5 attend pre-school, it is assumed that this intervention has the potential to reach the total population. Moreover, this intervention targeted pre-schoolers not because they have a particular higher risk to become obese

adults compared to for example adolescents, but rather because it is important to learn healthy habits in young-aged children as it has been shown that childhood behaviour may track to adulthood (Busschaert et al., 2015; Craigie, Lake, Kelly, Adamson, & Mathers, 2011; Friedman et al., 2008).

The subsequent interventions included in this PhD-thesis within the universal prevention category cover the prevention of skin cancer in Belgium. Skin cancer affects nearly 1 in 5 persons in Belgium. The global incidence of skin cancer -basal cell carcinoma, squamous cell carcinoma and melanoma- continues to increase, due to demographic factors (ageing of the population), but also due to environmental factors (such as the atmospheric ozone) and behavioural factors (such as going on holiday more often or getting a check-up more frequently). UV radiation is the most preventable cause of all major types of skin cancer. Avoiding excessive UV exposure, use of sunscreen and protective clothing are effective preventive measures. Therefore, we evaluated the cost-effectiveness and budget impact of the implementation of a *comprehensive national sensitising prevention campaign* in Belgium. This intervention strategy has been shown to prevent skin cancer by reducing the incidence of sunburn (Hill, White, Marks, & Borland, 1993). Not only natural but also artificial UV radiation can cause skin cancer. Lately, sunbed bans are a topic of debate in several countries and up to now only Australia and Brazil have recently implemented such a total ban. In this PhD-research, the cost-effectiveness of implementing a *total ban on sunbed use* in Belgium was evaluated.

The next interventions are classified as **selective prevention** as it concerns three interventions that restrict their target population to those assumed to be at increased risk to develop cancer. Many cancers -believed to be about 40%- can be prevented, some others can be detected at an early pre-clinical (or in some cases even pre-cancerous) stage, when there is high potential for cure. The greatest proportion of cancer deaths in Europe are attributable to lung, breast, colorectal, and prostate cancer (Ferlay et al., 2013). In Flanders, a population-based breast cancer screening program has been organised since 2001 and a colorectal cancer screening program since 2013. The cost-effectiveness of these screening programs have never been evaluated before. That is why in this thesis, the cost-effectiveness and the budget impact of both programs were assessed. Up to now, only few studies exist on the early detection of skin cancer. Based on a skin cancer screening trial organised in 2014 in two comparable regions in Belgium (Hoorens et al., 2016), the cost-effectiveness and budget impact of a one-time skin cancer screening were evaluated. The study considered two screening interventions, namely *a one-time total body examination and a one-time lesion-directed screening*. In the cost-effectiveness analysis, the results of this one-time screening were extrapolated to the Belgian population. Although the total-body examination is a universal prevention intervention, it was evaluated together with the lesion-directed screening intervention in one study. Therefore, both evaluations will be reported in the section of selective prevention interventions.

A final intervention evaluated in this thesis was categorised as **indicated prevention***,* targeting high-risk persons with suicidal thoughts. In 2012, suicide was reported to be the thirteenth leading cause of death in Europe (WHO, 2014b). The suicide rate in Belgium is almost one third higher than the European average (OECD, 2012d). However, currently there is a lack of studies providing evidence on the effectiveness and cost-effectiveness of interventions for suicide prevention (Scott & Guo, 2012), particularly suicide helplines (Krysinska & De Leo, 2007). The suicide helpline in Flanders, called ‘De

Zelfmoordlijn', has been set up in 1979, first by telephone and since 2005 it also offers chat sessions. In our study, the cost-effectiveness and budget impact of this suicide helpline was calculated.

The third and final part of this thesis comprises the general discussion which summarises and reflects on the included studies, in terms of health economic results as well as the experienced methodological challenges. These findings will be put in a broader perspective and recommendations for researchers, policy makers and other stakeholders who may be funding, participating in, or making use of economic evaluations are discussed.

Part 2: Original research studies: health economic evaluations in the continuum of prevention

2.1. Universal prevention interventions

2.1.1. Establishing a method to estimate the cost-effectiveness of a kindergarten-based, family-involved intervention to prevent obesity in early childhood. The ToyBox-study

Based on:

Pil L, Putman K, Cardon G, De Bourdeaudhuij I, Manios Y, Androutsos O, Lateva M, Iotova V, Zych K, Góźdź, González-Gil EM, De Miguel-Etayo P, Geyer C, Birnbaum J, Annemans L; The ToyBox-study group (2014). Establishing a method to estimate the cost-effectiveness of a kindergarten-based, family-involved intervention to prevent obesity in early childhood. The ToyBox-study. *Obesity Reviews, 15 Suppl 3,* 81-89

ABSTRACT

Overweight and obesity in children are recognised as a major health problem. The ToyBox-intervention was developed with the aim of preventing obesity in pre-schoolers. Because it is increasingly important to inform policy makers not only on the effects of prevention interventions, but also on their costs and cost-effectiveness, our purpose was to establish a method to estimate the cost-effectiveness of the ToyBox-intervention. In order to estimate the long term impact of the ToyBox-intervention on health and societal costs, extrapolations of the intervention effect will be conducted to predict children's weight status (based on the body mass index) at adult age. Effects of the adult weight status on the prevalence of obesity-related complications will be modelled through a Markov model, with a total time horizon of 70 years and a cycle length of 1 year. The analyses will be performed separately for six European countries participating in the ToyBox-intervention, based on country-specific economic and epidemiological data. This study describes the methodological rationale and implementation of an analytic model to examine the cost-effectiveness of the ToyBox-intervention, in order to inform policy makers on the value for money of this intervention in the prevention of obesity in pre-schoolers.

INTRODUCTION

The prevalence of overweight and obesity in pre-schoolers has substantially increased worldwide (De Onis, Blossner, & Borghi, 2010). Non-active lifestyles and non-healthy eating patterns have an important impact on this trend (Acosta et al., 2008; Liebman et al., 2003). Published literature has shown that obese children have a higher risk to be obese at adult age (Herman, Craig, Gauvin, & Katzmarzyk, 2009; Venn et al., 2007) and that obesity in children is associated with a higher risk for later chronic diseases such as heart disease (Baker et al., 2007). The trend of increasing prevalence of overweight and obese children and adults results in a rising societal impact due to higher health care costs and productivity loss (Konnopka, Bodemann, & Konig, 2011; Kwaliteitsinstituut voor de gezondheidszorg CBO, 2008). The ToyBox-study (short for 'Multifactorial evidence based approach using behavioural models in understanding and promoting fun, healthy food, play and policy for the prevention of obesity in early childhood') aimed to develop, implement and evaluate a kindergarten-based, family-involved intervention to prevent obesity in early childhood (Manios et al., 2012). Cost-effectiveness studies of health (care) programs are needed in order to inform policy makers on the value for money of a particular program (Cawley, 2007; Wang et al., 2008). Although the ToyBox-intervention effect is not yet evaluated, the current paper describes the design and data inputs of the health economic model used to estimate the long term costs and potential health effects of implementing the ToyBox-intervention, in the six intervention countries, namely, Belgium, Bulgaria, Germany, Greece, Poland and Spain.

METHODS

The ToyBox-intervention

The ToyBox-intervention was a randomised cluster trial which was implemented throughout the academic year 2012–2013 in Belgium, Bulgaria, Germany, Greece, Poland and Spain (Manios et al., 2012; Manios, 2012; Manios et al., 2014). The intervention targeted four key health behaviours, found to be associated with early obesity, in pre-schoolers aged 3.5-5.5 years old, namely drinking behaviour, snacking behaviour, physical activity and sedentary behaviour. Teachers from recruited kindergartens, assigned to the intervention group, were expected to make environmental changes in the classroom/kindergarten, such as installation of water stations and the 'magic snack plate', and to promote the four targeted energy balance-related behaviours (EBRBs) in the classroom/kindergarten, by for example implementing interactive classroom activities, for minimum 1 hour per week. Three training sessions were organised in order to provide detailed information to the teachers on how to implement the intervention (Androutsos et al., 2014b). Besides, parents were encouraged to apply relevant environmental and social changes at home, by means of newsletters, tip cards and posters that the children took home. More information on the design the study can be found in Manios et al. (2014). Alongside the intervention, a health economic evaluation will be conducted, estimating the long term costs and health benefits of the ToyBox-intervention.

Model structure

The health economic model developed for the ToyBox-intervention is a combined model consisting of a decision analytic model to represent either the probability of improved EBRBs or improved weight status (based on body mass index (BMI)) and a Markov model simulating over a lifetime the occurrence of obesity-related complications with and without the intervention. The target population of the model consists of European pre-schoolers, between 3.5 and 5.5 years old. The difference in costs over a period of 70 years will be divided by the net effects (in quality-adjusted life years, QALYs) to obtain the primary outcome measure, the incremental cost- effectiveness ratio: (Costs $^{\text{intervention group}}$ – Costs $^{\text{control group}}$) / (QALYs $^{\text{Intervention group}}$ − QALYs $^{\text{control group}}$).

There are three effect scenarios based on the possible anticipated consequences of the intervention: an effect either on the key EBRBs of the pre-schoolers targeted in the ToyBox-intervention (snacking behaviour, drinking behaviour, physical activity, sedentary behaviour), on anthropometric measures of the pre-schoolers or on both (Figure 1a). As chronic diseases start to develop at adult age, a long term extrapolation of the effect of the ToyBox-intervention on the pre-schoolers' EBRBs or on the pre-schoolers' anthropometrics to the adult age is necessary. Currently no studies are available that investigated the direct association between pre-schoolers' health behaviour and obesity-related diseases at adult age, hence the extrapolation needs to be made through adult weight status[10]. The effect scenario and the long term extrapolation make up the first part of the model. The second part of the model is a Markov model simulating the incidence of the main chronic diseases associated with obesity (type 2 diabetes, stroke, coronary heart disease (CHD), breast cancer, colorectal cancer) and mortality from the age of 30 years onwards (Figure 1b). For the first part of the model, tracking studies will be used that estimate the relationship between EBRBs or anthropometrics at pre-school age, on the one hand, and the weight status at adult age on the other hand. If anthropometric measures and/or healthy EBRBs in childhood improve as a consequence of the ToyBox-intervention, this will result in a shift in the prevalence of overweight or obesity at adult age. The relationship between weight status at adult age and obesity-related complications is obtained from the International Association for the Study of Obesity (2013). Hence, the impact on those obesity-related complications (and associated costs) at older age with the early childhood intervention can be calculated indirectly.

Extrapolation to adult weight status

<u>First scenario: effect on weight status of the pre-schoolers</u>

A first approach is modelling the (possible) intervention effect on the weight status of the children (i.e. change in the proportions of pre-schoolers who are normal weight, overweight or obese[11]), whereby we make use of the tracking study of Venn et al. (2007) to estimate the proportions of pre-schoolers that will be normal weight, overweight or obese at adult age based on their pre-school weight post-

[10] According to the WHO norms: normal weight: <25 kg m^2; overweight: 25.0-29.9 kg m^2; obese: ≥30 kg m^2 (WHO, 2013).

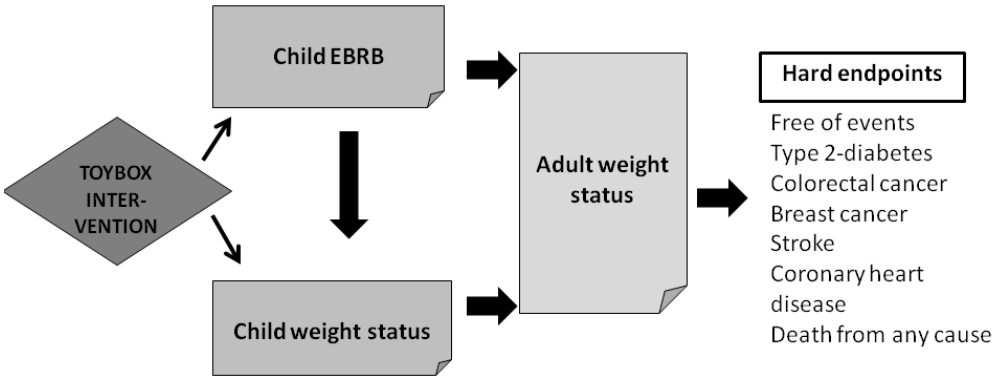
[11] According to the cut-off values developed by Cole et al. (2000), adopted by the International Obesity Task Force

intervention. In this way the (possible) intervention effect on weight status can be extrapolated from pre-schooler age to adult age.

Second scenario: effect on pre-schoolers' energy balance-related behaviours

A second approach is the modelling based on change in the EBRBs. If the ToyBox-intervention would have an effect on the EBRBs of the children that are targeted in the ToyBox-intervention, two methods could be used to extrapolate the effect to the adult weight status (Figure 1a). Dependent on the available evidence in published literature, the effect on childhood behaviours can be extrapolated directly to the weight status at adult age, or indirectly via weight status at mid-term child age (De Coen, De Bourdeaudhuij, Verbestel, Maes, & Vereecken, 2013; Dubois, Farmer, Girard, & Peterson, 2007).

Figure 1a: Model structure: extrapolation of the two possible intervention effects to the weight status at adult age (30-34 years) and the long term effect on the prevalence of the chronic diseases



EBRB: Energy balance-related behaviour; Narrow arrows: intervention effect; broad arrows: modelling.

Effect of the intervention: relative risk reduction

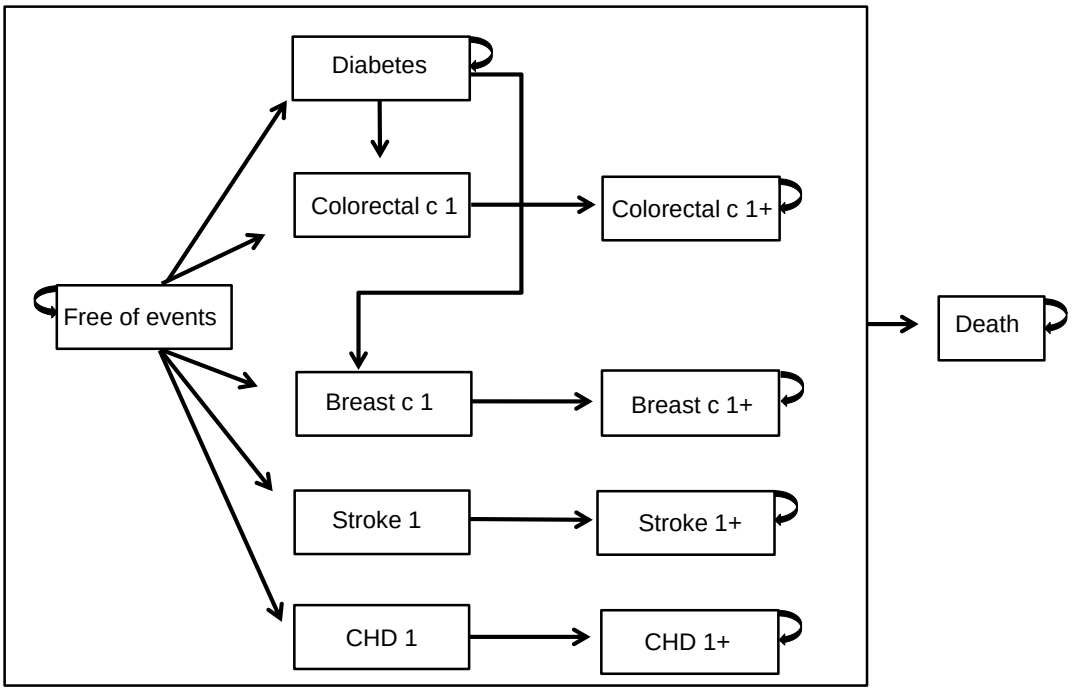
The effect of the intervention in the total sample (on the EBRBs or on the weight status of the pre-schoolers) will be extrapolated and modelled to the adult weight status. Hence, this intervention effect will be calculated as the relative risk reduction (RRR) in adult overweight/obesity in the intervention group, compared to the control group. This RRR will then be applied to the country-specific probabilities of the weight categories in the general adult population (Eurostat, 2008a), which is the starting population for the Markov model.

Modelling to the disease states

The Markov model includes the following states: 'free-of- events', type 2 diabetes, colorectal cancer, breast cancer (in females), stroke, CHD and death from any cause (Figure 1b). All events, except type 2 diabetes, consist of a first year state and a follow-up state, as these follow-up states are associated with different quality-of-life levels and costs. The model has a 1-year cycle, i.e. transitions between states are allowed once a year. All individuals in the Markov model target population start the model in

the age-category 30-34 years in the free-of-events state. At the end of the first year, individuals remain event free or move to one of the event states, based on the weighted average disease incidences (cf. infra). The first year in colorectal cancer, breast cancer, stroke and CHD are transitional states, i.e. one could only remain for one cycle in this state, after which one moves to the follow-up state or dies. Recurrence while being in follow-up is accounted for in the cost- and quality of life-measures. All individuals from the target cohort stay in the model until they die or until they reach the age of 100. Ten age categories are integrated in the model. Every age category and gender is associated with specific state transition probabilities. It should be taken into account that this model is a simplification of real life as suffering from more than one of the included chronic diseases at a time is not allowed in the model.

Figure 1b: Model design: Markov model of health states and possible transitions between them during each 1-year cycle.



1 = first year after diagnosis; 1+ = follow-up year; CHD = coronary heart disease

Transition probabilities

Age- and gender-dependent transition probabilities to the disease states are calculated based on country-specific disease incidences (Appendix Table 1), mortality rates and relative risks of the different weight categories on a particular disease (Table 1). The same relative risk estimates for each disease are applied to all countries, assuming there is no interaction between the weight status of an adult person and that person's country of residence on the associations (International Agency for Research on Cancer, 2002). Also, it was assumed that the relative risk estimates are the same for all age groups, except for breast cancer, where the distinction is made between premenopausal (<50 years) and postmenopausal breast cancer (>50 years). Based on these relative risk estimates, the disease

incidence associated with the different weight categories is calculated from the average country-specific disease incidence. The weighted averages of these specific incidences, making use of the Eurostat weight status probabilities (Eurostat, 2008a), is used as transition probabilities to the disease states. Hence, if the proportions in the adult weight status categories would change because of the ToyBox-intervention, then the weighted average disease incidence will change.

Table 1: Relative risks on chronic diseases for overweight and obese adults, in reference to normal weight adults, separately for males and females

Disease	Relative risk			
	overweight		obesity	
	males	females	males	females
Diabetes	2.25	2.30	5.50	7.00
Colorectal cancer	1.20	1.08	1.40	1.10
Breast cancer	1.00		1.00	
premenopausal (<50 years)		1.00		1.00
postmenopausal (≥50 years)		1.12		1.25
Stroke	1.20	1.20	1.50	1.55
Coronary heart disease	1.35	1.35	2.00	2.00

(International Association for the Study of Obesity, 2013)

Cost data

The health economic analysis will assume a societal perspective, i.e. including both the costs to the health care sector as well as costs related to productivity loss. Therefore, costs related to the disease states are split into direct medical costs for the health care sector and 'indirect' productivity related costs, the latter using the friction cost method, as explained further (Koopmanschap & van Ineveld, 1992). To calculate the cost of the intervention, all costs that are directly incurred by the intervention are included. The reference year of all costs is 2012, corresponding to the year of the start of the ToyBox-intervention.

Intervention costs

The country-specific cost of the ToyBox-intervention is calculated, based on the cost of the ToyBox material and delivery (cost of the design and production process not included), the cost of the teacher training sessions and other implementation attributable expenses such as transport to the kindergartens for trainings and the extra time spent by teachers on the intervention (beyond the class time, such as reading, preparing, talking to parents). In total three training sessions (conducted by the research staff) were organised for the teachers in order to train them for implementing the intervention as accurately as possible and to evaluate their experiences at different time points (Androutsos et al., 2014b). According to the method described by Kesztyus et al. (2013), costs for the development of the intervention materials as well as costs for the scientific evaluation are not included, and only costs that would be incurred by a repeated implementation are assessed. No costs were assigned to the control groups.

Each intervention class received one plastic box, including material for 25 pre-schoolers/families, namely, eight tip cards for the parents/caregivers (two per behaviour), nine newsletters for the parents/caregivers (one general + two per behaviour), four posters (one per behaviour), one binder with five types of handbooks for the teacher: one teacher general guide, four classroom activity guides, i.e. one for each of the targeted behaviours, and one hand puppet (De Craemer et al., 2014; Duvinage et al., 2014). A total cost for material boxes is assigned to every school, based on the amount and size of intervention classes per school.

The costs related to the training sessions include direct travel costs to the venue of training sessions for teachers as well as trainers, time spent in travel, duration of the sessions and extra costs related to catering, renting the venue and possible incentives for teachers (Androutsos et al., 2014b). These costs were recorded via training session questionnaires by the ToyBox research staff and the teachers. Monthly diaries, filled out by the ToyBox research staff, captured the time ToyBox research staff spent on the preparation of the sessions. Time teachers spent on the training session (transport to and duration of the training) was calculated via ToyBox research staff's and teachers' training reports, filled out after every session by the teachers and the ToyBox research staff. Missing data of teachers on means of transport, amount of kilometers and time spent on transport were imputed using averages of the available information for that country. Average salary costs (gross salary + contribution of the employer) of kindergarten teachers and research staff (with on average 2-3 years of experience) were obtained from the partner countries. The salary cost related to classroom time of teachers was not included in the intervention as we assume that this is not extra invested time. However, the extra time teachers have spent on the ToyBox-intervention is captured in the cost calculation as well as the time teachers were at a training session (duration of the training and time spent on transport).
To calculate other implementation-related costs, such as labour costs and transportation costs of teachers and research staff during the intervention months (besides training sessions), diaries and transport questionnaires were compiled and filled out by all research staff of each country. Transportation costs were based on the average refund for work-related car expenses. Process evaluation tools (teachers' training evaluation forms and monthly logbooks) were used to assess the costs associated with the teachers (extra time spent and extra material bought) (Androutsos et al., 2014a). Labour costs of teachers were based on the average gross salary.

The country-specific cost of the intervention is expressed as an average cost per 1,000 pre-schoolers (Table 2). In total 68, 41, 126, 137, 63 and 47 intervention classes, respectively in Belgium, Bulgaria, Germany, Greece, Poland and Spain participated in the ToyBox-study. As explained before, every intervention class received a box of materials. The cost of the box was obtained from the manufacturer (AOK-Verlag) and amounted to €45.2 per box. Delivery cost of the material boxes ranged from €2.2 to €11.2 per school delivery. The work-related kilometer refund, used in the calculations of the transport cost, in Belgium, Bulgaria, Germany, Greece, Poland and Spain, was respectively €0.35, €0.15, €0.35, €0.2, €0.17 and €0.19 per kilometer. The price per one-way ticket of public transport was, respectively €1.2, €0.51, €2.5, €1.4, €0.88 and €1.25. The total cost related to the trainings sessions (transport and labor cost) for research staff and teachers was respectively €3,755 and €917 in Belgium, €488 and €1,332 in Bulgaria, €8,110 and €6,111 in Germany, €3,223 and €6,942 in Greece, €1,326 and €1,948

in Poland, and €815 and €844 in Spain. The greatest contributors to the total training session cost, per 1,000 pre-schoolers, in Greece, Poland and Spain was the labor cost of the teachers, in Belgium and Germany the labor cost of the research staff, and in Bulgaria the extra costs -for extra materials and services during the training sessions.

Table 2: Country-specific intervention costs (in 2012 euro)

	Belgium	Bulgaria	Germany	Greece	Poland	Spain
Material boxes	€ 3,076	€ 1,854	€ 5,699	€ 6,873	€ 2,827	€ 2,126
Delivery of material boxes	€ 168	€ 69	€ 200	€ 136	€ 172	€ 136
Transport study staff for training sessions	€ 874	€ 41	€ 1,262	€ 177	€ 98	€ 15
Transport teachers for training sessions	€ 182	€ 562	€ 1,409	€ 1,764	€ 208	€ 119
Labor cost study staff for training sessions	€ 2,881	€ 457	€ 6,848	€ 3,046	€ 1,228	€ 800
Labor cost teachers for training sessions	€ 735	€ 770	€ 4,702	€ 5,178	€ 1,740	€ 725
Extra costs for training sessions	€ 16	€ 1,473	€ 126	€ 801	€ 0	€ 0
Labor cost study staff intervention months	€ 1,894	€ 699	€ 5,369	€ 4,823	€ 1,487	€ 1,699
Labor costs teachers intervention months	€ 3,272	€ 714	€ 10,905	€ 8,538	€ 484	€ 2,642
Transport cost study staff intervention months	€ 416	€ 79	€ 0	€ 456	€ 43	€ 170
Extra costs teachers intervention months	€ 564	€ 350	€ 2,211	€ 1,661	€ 25	€ 1,116
Number of kids receiving the intervention material	1243	1164	1343	3132	1584	1068
Total cost per 1,000 pre-schoolers	**€ 11,325**	**€ 6,074**	**€ 28,840**	**€ 10,681**	**€ 5,248**	**€ 8,940**

Costs per disease state

Costs per disease state in the model are derived from national and international sources, to obtain country-specific annual costs per person per disease state (Table 3). Direct medical costs as well as indirect economic costs (due to productivity loss) are captured in the model. To take into account the prevalence of diabetes in people with breast cancer or colorectal cancer, 23.8% of the total diabetes cost was added to the total cost of breast cancer and 38.2% of the total diabetes cost was added to the total cost of colorectal cancer (Sanchez Peralta, Oliveras-Lopez, Perez, Martinez, & Lopez-Garcia de la Serrana, 2012). To calculate indirect costs due to morbidity and mortality, the friction cost method is used. This method states that 'disease may cause losses in production, but in general this loss will be confined to a period needed to adapt to the changed situation of work absence' (Koopmanschap & van Ineveld, 1992). To calculate the cost of death, an average friction period length of 160 days, based on the report of Hakkaart-van Roijen and colleagues (2010), is multiplied by the average cost of one day absenteeism (Securex, 2010). The indirect cost per disease state is calculated based on the ratio of

total and direct cost derived from Dutch literature (making use of the friction cost method). This ratio is applied to the disease states in every country. These indirect costs are only applied to productive age categories (30-65 years) and accounting for the average unemployment rate per country. As future costs and benefits are of less value than current cost and benefits, discounting future values to present values is applied. Annual discount rates of 3% and 1.5% are applied to future costs and effects respectively, as recommended by the Belgian Knowledge Centre for Health care (Cleemput et al., 2012). If costs for certain disease states were unavailable for some countries, they were imputed by the multiple imputation procedure in the statistical software program STATA, StataCorp, College Station, Texas, USA.

Quality-of-life data

QALYs are calculated by multiplying the utility level for a given condition (a health-related quality-of-life weight ranging between 0 and 1) with the numbers of years an individual lives with the particular condition. A utility of 1 is equal to perfect health, whereas 0 stands for death. Per country, age-specific EQ-5D utilities (i.e. quality-of-life indices used to calculate QALYs) per first year state and per follow-up year state were obtained from published literature (Table 4). The overall life satisfaction of people seems to be clustered in regions (Eurostat, 2015b), showing no big differences between the participating countries, except for Bulgaria. Therefore, if utilities for a certain state were not available for the particular country, published utilities from a nearby country were used. For Bulgaria, no utility data was available. Therefore, we used the utility data applied to the Belgian case, applying a ratio of 0.7 (Eurostat, 2015b).

Sensitivity analyses

One-way and probabilistic sensitivity analyses will be conducted to capture uncertainty in the main parameters. The individual effect of the intervention cost, total costs per disease state, the intervention effect, the relative risk of tracking for overweight and for obesity from childhood to adulthood, the relative risk of adult overweight and obesity on obesity-related diseases, disease incidence and the utilities per disease state will be evaluated in case of better or worse conditions of these parameters -defined by the confidence interval or ±30% variation in case confidence intervals were absent. A probabilistic analysis will vary these parameter values simultaneously by their own probability distribution. Cost data are assumed to be distributed according to a gamma-distribution, disease incidence and utilities according to a beta-distribution and relative risks according to a log-normal distribution (Briggs et al., 2006).

Table 3: Annual country-specific direct and indirect costs associated with the model diseases (per person).

	Belgium[1]	Bulgaria[2]	Germany[3]	Greece[4]	Poland[5]	Spain[6]
Direct cost diabetes	€ 3,038	€ 1,790*	€ 3,038	€ 1,502	€ 1,574	€ 2,938
Indirect cost diabetes	€ 619	€ 345	€ 631	€ 257	€ 301	€ 485
Direct costs CRC	€ 25,451	€ 4,375*	€ 31,008	€ 24,677*	€ 7,038	€ 27,395*
Indirect costs CRC	€ 16,494	€ 2,683	€ 20,501	€ 13,422	€ 4,287	€ 14,377
Direct cost CRC FU	€ 8,596	€ 2,536*	€ 6,452	€ 6,310*	€ 7,038	€ 12,158*
Indirect cost CRC FU	€ 5,571	€ 1,555	€ 4,266	€ 3,432	€ 4,287	€ 6,380
Direct cost BC	€ 13,156	€ 9,516*	€ 34,663*	€ 23,329*	€ 8,741	€ 16,707
Indirect cost BC	€ 8,648	€ 5,837	€ 22,917	€ 12,689	€ 5,324	€ 8,768
Direct cost BC FU	€ 3,171	€ 7,843*	€ 11,223*	€ 9,182*	€ 8,741	€ 3,001
Indirect cost BC FU	€ 2,055	€ 4,810	€ 7,420	€ 4,994	€ 5,324	€ 1,575
Direct cost stroke	€ 11,531	€ 881	€ 21,227	€ 5,780	€ 2,989	€ 6,151
Indirect cost stroke	€ 854	€ 54	€ 1,403	€ 314	€ 182	€ 323
Direct cost stroke FU	€ 4,882	€ 275	€ 6,281	€ 3,000	€ 1,096	€ 2,525
Indirect cost stroke FU	€ 316	€ 17	€ 415	€ 163	€ 67	€ 133
Direct costs CHD	€ 6,001	€ 1,368	€ 5,975	€ 6,418	€ 1,394	€ 5,325*
Indirect cost CHD	€ 389	€ 84	€ 395	€ 349	€ 85	€ 279
Direct cost CHD FU	€ 1,658	€ 474	€ 1,019	€ 3,000	€ 465	€ 2,072*
Indirect cost CHD FU	€ 107	€ 29	€ 67	€ 163	€ 28	€ 109
Cost death	€ 44,800	€ 4,684	€ 45,163	€ 26,159	€ 11,734	€ 28,798

BC = breast cancer; CRC = colorectal cancer; FU= follow-up; * Imputed costs

1 (Annemans, Lamotte, Clarys, & Van den Abeele, 2007; Hakkaart-van Roijen, 2010; Lamotte, Annemans, Evers, & Kubin, 2006; Pacolet, De Coninck, Hedebouw, Cabus, & Spruytte, 2011; Securex, 2010; Steuten et al., 2007; Van Gelder & Annemans, 2011; Williams, Van, & Lucioni, 2002)

2 (De Smedt et al., 2012; Kimman et al., 2011; Leal et al., 2006; Steuten et al., 2007)

3 (Cook et al., 2004; Haug, Engel, Linder, & Verheyen, 2012; Kimman et al., 2011; Leal et al., 2006; Steuten et al., 2007; Williams et al., 2002)

4 (Athanasakis et al., 2010; Fragoulakis, Kourlaba, & Maniadakis, 2012; Kimman et al., 2011; Leal et al., 2006; Steuten et al., 2007)

5 (Carles et al., 2011; Dane i analizy, 2010; De Smedt et al., 2012; De Smedt et al., 2013; Kimman et al., 2011; Kinalska et al., 2003; Leal et al., 2006; Steuten et al., 2007)

6 (Ballesta, Carral, Olveira, Giron, & Aguilar, 2006; Carles et al., 2011; Kimman et al., 2011; Leal et al., 2006; Lopez-Bastida et al., 2012; Steuten et al., 2007)

Table 4: ranges of utilities per country, dependent on age, used to calculate the adjusted quality of life-years.

	Belgium[1]	Bulgaria[2]	Germany[3]	Greece[4]	Poland[5]	Spain[6]
Free of events	0.68-0.84	0.48-0.59	0.86-0.94	0.65-0.92	0.76-0.94	0.67-0.94
Diabetes	0.52-0.70	0.34-0.46	0.73-0.81	0.49-0.76	0.47-0.65	0.49-0.76
CRC	0.45-0.63	0.29-0.41	0.49-0.57	0.42-0.69	0.40-0.58	0.33-0.60
CRC FU	0.37-0.64	0.31-0.42	0.52-0.60	0.45-0.72	0.43-0.60	0.37-0.64
BC	0.65-0.83	0.43-0.55	0.69-0.77	0.62-0.89	0.60-0.78	0.53-0.80
BC FU	0.68-0.86	0.45-0.56	0.72-0.80	0.65-0.92	0.63-0.81	0.60-0.87
Stroke	0.47-0.65	0.31-0.42	0.59-0.67	0.38-0.65	0.49-0.67	0.40-0.67
Stroke FU	0.51-0.69	0.33-0.45	0.63-0.71	0.48-0.75	0.46-0.64	0.30-0.57
CHD	0.54-0.79	0.27-0.38	0.66-0.74	0.53-0.80	0.41-0.59	0.47-0.74
CHD FU	0.61-0.79	0.40-0.52	0.70-0.78	0.59-0.86	0.57-0.75	0.50-0.77

CRC = colorectal cancer; BC = breast cancer; CHD = coronary heart disease; FU = follow up

1 (De Smedt et al., 2013; Dorman, Dennis, & Sandercock, 2000; Heyworth, Hazell, Linehan, & Frank, 2009; Kimman et al., 2011; Kramer et al., 2012; Stouthard, Essink-Bot, & Bonsel, 2000; Scientific Institute of Public Health., 2013; Whynes, 2013; Wiering et al., 2010)

2 Sources used for Belgium * 0.7 (based on the information from Eurostat (Eurostat, 2015b))

3 (De Smedt et al., 2013; Haacke et al., 2006; Kimman et al., 2011; Kramer et al., 2012; Ose et al., 2009; Schweikert et al., 2009; Stouthard et al., 2000; Whynes, 2013; Wiering et al., 2010)

4 (Dorman et al., 2000; Heyworth et al., 2009; Kimman et al., 2011; Kontodimopoulos et al., 2008; Spiraki, Kaitelidou, Papakonstantinou, Prezerakos, & Maniadakis, 2008; Stouthard et al., 2000; Whynes, 2013; Wiering et al., 2010)

5 (De Smedt et al., 2013; Dorman et al., 2000; Golicki, Niewada, Jakubczyk, Wrona, & Hermanowski, 2010; Heyworth et al., 2009; Jegier et al., 2009; Kimman et al., 2011; Stouthard et al., 2000; Whynes, 2013; Wiering et al., 2010)

6 (Cunillera et al., 2010; De Smedt et al., 2013; Kimman et al., 2011; Kramer et al., 2012; Lopez-Bastida et al., 2012; Mata Cases, Roset Gamisans, Badia Llach, Antonanzas Villar, & Ragel Alcazar, 2003; Moro-Valdezate et al., 2013; Stouthard et al., 2000; Whynes, 2013; Wiering et al., 2010)

DISCUSSION

The ToyBox-intervention is a kindergarten-based, family- involved intervention, focusing on pre-school snacking and drinking behaviour, physical activity and sedentary behaviour (Manios et al., 2014). Obesity prevention provides a major opportunity to improve population health. As health improvements usually require additional and scarce resources, novel interventions should be economically evaluated (Lehnert, Sonntag, Konnopka, Riedel-Heller, & Konig, 2012). The current paper described the methods and the data inputs for the cost-effectiveness analysis of the ToyBox-intervention. In the prevention of obesity, health benefits may slowly accumulate over time. The aim of the cost-effectiveness analysis is to estimate the long term impact of the ToyBox-intervention on the prevalence of obesity-related complications in comparison with current practice (i.e. no ToyBox-intervention). This will result in estimates of the long term costs or savings and health benefits in six European countries where the intervention was implemented, to inform policy makers about whether the intervention is worth the money. Extrapolations of the intervention effect to the adult age are necessary because, in general, chronic diseases start to develop at adult age. We tried to collect country-specific information on costs,

disease incidences and quality-of-life data. The intervention cost captures all expenses associated with implementing the intervention, including the cost for personnel and teachers, training sessions, transportation of training personnel and teachers, intervention materials and extra materials if necessary. The same method was used in other cost-effectiveness analyses of school-based prevention programs such as the study of Wang et al. (2008). The largest part of the intervention cost was due to personnel costs (labor cost of research staff and teachers), accounting for on average 58% of the total cost. Wang et al. observed a similar pattern, with 63% of the total intervention cost spent on personnel (2008). Differences in the cost for the material between countries (Germany and Greece versus Belgium, Bulgaria, Poland and Spain) were due to the fact that in Germany and Greece there were more participating classes, and in Germany these classes consisted on average of less pre-schoolers (on average 11 versus 23 in the other countries). The higher costs for training sessions in Greece and Germany were due to the fact that the teachers had spent much time to the transportation to the training sessions in reference to the other intervention countries and because the researchers had spent more time per teacher to the training session and to transportation in reference to the other intervention countries. The higher other implementation-related expenses in Greece and Germany were caused by teachers and researchers spending more (extra) time to the intervention in reference to the other intervention countries. However, because there were more participating pre-schoolers in Greece than in Germany, the total intervention cost per 1,000 pre-schoolers is much lower in Greece in reference to Germany. The total intervention cost in Poland and Bulgaria was low in reference to the other countries, mainly because of the low personnel costs. Literature on country-specific direct medical costs of the included diseases in our model is very scarce. Therefore, many different sources and data sets had to be consulted and missing data had to be statistically imputed. It is possible that the disease costs in the countries included in our study captured different medical acts, but this was not always reported. However, the differences between the countries in the annual costs per disease state (Table 3) reflect the variations in per capita gross domestic product (GDP). Only for breast cancer there are no big differences in cost between Bulgaria and Poland, on the one hand, and Belgium, Germany and Greece, on the other hand. This could be due to the fact that other types of costs are included in the direct medical cost of breast cancer in the first two countries; however, this was not clearly reported.

Until now, this is the first cross-European intervention aiming to prevent obesity in pre-schoolers and to assess its cost-effectiveness. The general method for calculating the cost-effectiveness of such a health promoting program, namely taking into account the generated health effect in the target group and the economic consequences for the society, and more specifically, the tracking method, namely the estimation of adult weight status based on childhood weight status/EBRBs, has been reported previously in cost-effectiveness analyses of overweight programs (Brown et al., 2007; Hagberg & Lindholm, 2005). However, our study design can guide and inform other cost-effectiveness analyses of childhood obesity prevention programs as it also accounts for the anticipated potential effect of the intervention on EBRBs.

Nonetheless, there are some limitations to the analysis, due to its multicenter nature. First, as country-specific cost and quality-of-life data were not always available, some imputations had to be conducted for the direct cost of certain diseases. Second, a critical point in effectiveness and cost-effectiveness studies in the field of child health promotion is the use of BMI as a measure of child weight status, as it

does not distinguish between muscle mass and fat mass. In our health economic analysis of the ToyBox-intervention, we need to rely on literature reporting the link between child overweight/obesity and adult overweight/obesity, and the association of adult overweight/obesity with morbidity. However, as literature describing the relation between waist circumference - argued to be a better measure for overweight and obesity - and morbidity is scarce, weight status (based on BMI) was used as an effect measure. Finally, if the ToyBox-intervention would have an effect on children's EBRBs, some assumptions will have to be made concerning the extrapolation to adult age, as literature on the impact of EBRBs on later health and weight status is scarcer than literature on the impact of child weight status on later weight status. However, including more indirect relations into a model is associated with including more uncertainty. This uncertainty will be addressed in the cost-effectiveness analysis.

CONCLUSION

In summary, it is clear that early intervention efforts are needed to prevent obesity later in life. However, because financial resources are scarce, cost-effectiveness analyses are necessary to inform the choices of decision-makers. The aim of this study was to communicate an extensive description of the health economic model design and data inputs in order to better understand how the cost-effectiveness analysis of the ToyBox-intervention is performed and to guide other cost-effectiveness analyses of childhood obesity prevention programs.

APPENDIX

Appendix Table 1a: Age- and gender specific disease incidences in Belgium

	BELGIUM									
Males	**30-34y**	**35-39y**	**40-44y**	**45-49y**	**50-54y**	**55-59y**	**60-64y**	**65-69y**	**70-74y**	**75+**
Incidence diabetes[a]	0.09%	0.14%	0.21%	0.31%	0.44%	0.59%	0.74%	0.86%	0.92%	0.88%
Incidence colorectal cancer[b]	0.01%	0.01%	0.01%	0.03%	0.06%	0.11%	0.16%	0.27%	0.34%	0.49%
Incidence stroke[c]	0.03%	0.05%	0.07%	0.11%	0.17%	0.25%	0.37%	0.56%	0.84%	1.88%
Incidence CHD[d]	0.01%	0.07%	0.07%	0.20%	0.20%	0.59%	0.59%	0.73%	1.11%	1.11%

	BELGIUM									
Females	**30-34y**	**35-39y**	**40-44y**	**45-49y**	**50-54y**	**55-59y**	**60-64y**	**65-69y**	**70-74y**	**75+**
Incidence diabetes[a]	0.07%	0.10%	0.16%	0.23%	0.33%	0.45%	0.56%	0.65%	0.70%	0.64%
Incidence colorectal cancer[b]	0.00%	0.01%	0.01%	0.03%	0.04%	0.08%	0.11%	0.16%	0.20%	0.38%
Incidence breast cancer[b]	0.04%	0.09%	0.16%	0.25%	0.31%	0.34%	0.42%	0.41%	0.38%	0.37%
Incidence stroke[c]	0.03%	0.04%	0.06%	0.09%	0.13%	0.20%	0.29%	0.44%	0.66%	1.62%
Incidence CHD[d]	0.01%	0.01%	0.01%	0.13%	0.13%	0.12%	0.12%	0.17%	0.51%	0.51%

a Source: (Rijksinstituut voor Volksgezondheid, 2011a); b Source: (Belgian Cancer Registry, 2009); c Source: (Rijksinstituut voor Volksgezondheid, 2011b); d Source: (Van Herck et al., 2009)

Appendix Table 1b: Age- and gender specific disease incidences in Bulgaria

	BULGARIA									
Males	**30-34y**	**35-39y**	**40-44y**	**45-49y**	**50-54y**	**55-59y**	**60-64y**	**65-69y**	**70-74y**	**75+**
Incidence diabetes[a]	0.10%	0.15%	0.23%	0.34%	0.49%	0.65%	0.82%	0.95%	1.03%	0.97%
Incidence colorectal cancer[b]	0.00%	0.00%	0.01%	0.03%	0.06%	0.12%	0.19%	0.26%	0.33%	0.35%
Incidence stroke[c]	0.34%	0.34%	0.34%	0.34%	0.34%	0.73%	0.73%	1.03%	1.03%	2.15%
Incidence CHD[a]	0.01%	0.11%	0.11%	0.29%	0.29%	0.86%	0.86%	1.06%	1.61%	1.61%

	BULGARIA									
Females	**30-34y**	**35-39y**	**40-44y**	**45-49y**	**50-54y**	**55-59y**	**60-64y**	**65-69y**	**70-74y**	**75+**
Incidence diabetes[a]	0.07%	0.11%	0.17%	0.26%	0.37%	0.49%	0.62%	0.72%	0.78%	0.71%
Incidence colorectal cancer[b]	0.00%	0.00%	0.01%	0.03%	0.05%	0.08%	0.11%	0.15%	0.18%	0.20%
Incidence breast cancer[b]	0.02%	0.02%	0.09%	0.12%	0.15%	0.17%	0.19%	0.20%	0.19%	0.19%
Incidence stroke[c]	0.09%	0.09%	0.09%	0.09%	0.09%	0.49%	0.49%	0.81%	0.81%	1.93%
Incidence CHD[a]	0.02%	0.03%	0.02%	0.14%	0.09%	0.29%	0.19%	0.32%	0.63%	0.61%

a Imputation based on diabetes prevalence; b (GLOBOCAN, 2008); c (Powles, Kirov, Feschieva, Stanoev, & Atanasova, 2002)

Appendix Table 1c: Age- and gender specific disease incidences in Germany

	GERMANY									
Males	**30-34y**	**35-39y**	**40-44y**	**45-49y**	**50-54y**	**55-59y**	**60-64y**	**65-69y**	**70-74y**	**75+**
Incidence diabetes[a]	0.41%	0.41%	0.41%	0.41%	0.41%	0.41%	0.41%	0.86%	0.86%	0.86%
Incidence colorectal cancer[b]	0.00%	0.00%	0.01%	0.03%	0.06%	0.11%	0.17%	0.25%	0.33%	0.44%
Incidence stroke[c]	0.01%	0.03%	0.03%	0.13%	0.13%	0.37%	0.37%	0.58%	0.58%	1.25%
Incidence CHD[d]	0.00%	0.04%	0.03%	0.23%	0.16%	0.87%	0.59%	0.76%	0.77%	0.73%

	GERMANY									
Females	**30-34y**	**35-39y**	**40-44y**	**45-49y**	**50-54y**	**55-59y**	**60-64y**	**65-69y**	**70-74y**	**75+**
Incidence diabetes[a]	0.22%	0.22%	0.22%	0.22%	0.22%	0.22%	0.22%	0.33%	0.33%	0.33%
Incidence colorectal cancer[b]	0.00%	0.00%	0.01%	0.02%	0.04%	0.06%	0.09%	0.12%	0.16%	0.27%
Incidence breast cancer[b]	0.02%	0.02%	0.10%	0.16%	0.22%	0.28%	0.34%	0.36%	0.27%	0.34%
Incidence stroke[c]	0.01%	0.02%	0.02%	0.15%	0.15%	0.24%	0.24%	0.48%	0.48%	1.05%
Incidence CHD[d]	0.01%	0.01%	0.01%	0.23%	0.15%	0.14%	0.10%	0.19%	0.37%	0.33%

a (Meisinger, Doring, Thorand, Heier, & Lowel, 2006; Rathmann et al., 2009); b (GLOBOCAN, 2008); c (Palm et al., 2010); d Imputation based on stroke incidence

Appendix Table 1d: Age- and gender specific disease incidences in Greece

	GREECE									
Males	**30-34y**	**35-39y**	**40-44y**	**45-49y**	**50-54y**	**55-59y**	**60-64y**	**65-69y**	**70-74y**	**75+**
Incidence diabetes[a]	0.00%	1.15%	1.15%	1.29%	1.29%	2.37%	2.37%	3.38%	3.38%	2.26%
Incidence colorectal cancer[b]	0.00%	0.00%	0.01%	0.01%	0.02%	0.04%	0.06%	0.09%	0.13%	0.23%
Incidence stroke[c]	0.02%	0.04%	0.04%	0.22%	0.22%	0.53%	0.53%	1.54%	1.54%	3.58%
Incidence CHD[d]	0.03%	0.06%	0.06%	0.33%	0.33%	0.81%	0.81%	2.34%	2.34%	5.44%

	GREECE									
Females	**30-34y**	**35-39y**	**40-44y**	**45-49y**	**50-54y**	**55-59y**	**60-64y**	**65-69y**	**70-74y**	**75+**
Incidence diabetes[a]	0.08%	0.85%	0.85%	1.44%	1.44%	2.48%	2.48%	2.19%	2.19%	3.59%
Incidence colorectal cancer[b]	0.00%	0.00%	0.01%	0.01%	0.02%	0.03%	0.04%	0.05%	0.07%	0.17%
Incidence breast cancer[b]	0.01%	0.01%	0.07%	0.08%	0.09%	0.11%	0.15%	0.16%	0.16%	0.26%
Incidence stroke[c]	0.01%	0.02%	0.02%	0.10%	0.10%	0.29%	0.29%	1.22%	1.22%	3.99%
Incidence CHD[d]	0.02%	0.04%	0.04%	0.17%	0.17%	0.50%	0.50%	2.11%	2.11%	6.91%

a (Panagiotakos, Pitsavos, Skoumas, Lentzas, & Stefanadis, 2008); b (GLOBOCAN, 2008); c (Truelsen et al., 2006); d (Panagiotakos, Pitsavos, Chrysohoou, Skoumas, & Stefanadis, 2008)

Appendix Table 1e: Age- and gender specific disease incidences in Poland

	POLAND									
Males	**30-34y**	**35-39y**	**40-44y**	**45-49y**	**50-54y**	**55-59y**	**60-64y**	**65-69y**	**70-74y**	**75+**
Incidence diabetes[a]	0.10%	0.15%	0.22%	0.33%	0.48%	0.64%	0.80%	0.93%	1.01%	0.95%
Incidence colorectal cancer[b]	0.00%	0.00%	0.01%	0.02%	0.05%	0.10%	0.17%	0.25%	0.32%	0.37%
Incidence stroke[c]	0.02%	0.03%	0.03%	0.25%	0.25%	0.61%	0.61%	1.26%	1.26%	1.66%
Incidence CHD[d]	0.00%	0.07%	0.07%	0.20%	0.20%	0.58%	0.58%	0.71%	1.08%	1.08%

	POLAND									
Females	**30-34y**	**35-39y**	**40-44y**	**45-49y**	**50-54y**	**55-59y**	**60-64y**	**65-69y**	**70-74y**	**75+**
Incidence diabetes[a]	0.07%	0.11%	0.17%	0.25%	0.36%	0.48%	0.61%	0.71%	0.76%	0.70%
Incidence colorectal cancer[b]	0.00%	0.00%	0.01%	0.02%	0.03%	0.05%	0.08%	0.11%	0.15%	0.20%
Incidence breast cancer[b]	0.01%	0.01%	0.06%	0.10%	0.14%	0.18%	0.22%	0.21%	0.19%	0.17%
Incidence stroke[c]	0.01%	0.03%	0.03%	0.10%	0.10%	0.29%	0.29%	0.80%	0.80%	1.63%
Incidence CHD[d]	0.01%	0.01%	0.01%	0.16%	0.11%	0.17%	0.12%	0.32%	0.62%	0.51%

a Imputation; b (GLOBOCAN, 2008); c (Truelsen et al., 2006); d Imputation

Appendix Table 1f: Age- and gender specific disease incidences in Spain

	SPAIN									
Males	**30-34y**	**35-39y**	**40-44y**	**45-49y**	**50-54y**	**55-59y**	**60-64y**	**65-69y**	**70-74y**	**75+**
Incidence diabetes[a]	0.85%	0.85%	0.85%	1.02%	1.02%	1.02%	1.52%	1.52%	1.52%	1.52%
Incidence colorectal cancer[b]	0.00%	0.00%	0.01%	0.03%	0.07%	0.12%	0.19%	0.27%	0.36%	0.46%
Incidence stroke[c]	0.02%	0.02%	0.02%	0.02%	0.02%	0.15%	0.15%	0.35%	0.35%	0.72%
Incidence CHD[d]	0.00%	0.02%	0.02%	0.03%	0.02%	0.36%	0.24%	0.46%	**0.47%**	0.42%

	SPAIN									
Females	**30-34y**	**35-39y**	**40-44y**	**45-49y**	**50-54y**	**55-59y**	**60-64y**	**65-69y**	**70-74y**	**75+**
Incidence diabetes[a]	0.85%	0.85%	0.85%	1.02%	1.02%	1.02%	1.52%	1.52%	1.52%	1.52%
Incidence colorectal cancer[b]	0.00%	0.00%	0.02%	0.03%	0.05%	0.07%	0.09%	0.13%	0.17%	0.24%
Incidence breast cancer[b]	0.02%	0.02%	0.10%	0.15%	0.17%	0.20%	0.22%	0.20%	0.21%	0.21%
Incidence stroke[c]	0.01%	0.01%	0.01%	0.01%	0.01%	0.04%	0.04%	0.27%	0.27%	0.57%
Incidence CHD[d]	0.01%	0.01%	0.01%	0.01%	0.01%	0.02%	0.02%	0.11%	0.21%	0.18%

a (Valdes, Botas, Delgado, Alvarez, & Cadorniga, 2007); b (GLOBOCAN, 2008); c (Vega et al., 2009); d Imputation

2.1.2. Cost-effectiveness analysis of a kindergarten-based, family-involved intervention to prevent obesity in early childhood. The ToyBox intervention

Lore Pil, An-Sofie Pinket, Delphine De Smedt, Koen Putman and Lieven Annemans. Cost-effectiveness analysis of a kindergarten-based, family-involved intervention to prevent obesity in early childhood. The ToyBox intervention. (*Working Paper).*

ABSTRACT

Background: Childhood obesity not only affects the current health status, but also has an impact on health later in life. It is associated with chronic obesity-related diseases at adult age, which also affects the health care expenditure. Prevention should focus on early age children, in order to tackle the obesity challenge. Evaluating the cost-effectiveness of such interventions informs the decision of policy makers. In this study, the cost-effectiveness of the Toy-Box intervention was evaluated.

Methods: A health economic model was developed consisting of a decision analytic model representing the intervention effect in the pre-schoolers and the projection of this intervention effect to adult age, followed by a Markov model simulating the occurrence of obesity-related complications in adults. Costs and quality-adjusted life-years were analysed over lifetime, in order to calculate the incremental cost-effectiveness ratio. Sensitivity analyses were performed, taking into account uncertainty of the model parameters.

Results: Assuming country-specific willingness-to-pay thresholds based on the gross domestic product, the ToyBox-intervention was estimated to be cost-effective in Spain (males: €21,719/QALY gained; 95%CI: €2,646 – €178,296. Females: €10,568/QALY gained; 95%CI €476 – €87,298) and Poland (the latter only in females: €6,304/QALY gained; 95%CI: €1,277 – €44,637) and borderline cost-effective in Greek and Belgian females (respectively: €20,279/QALY gained; 95%CI: €5,663 – €140,325 and €37,422/QALY gained; 95%CI: €12,357 – €234,296). The analysis included quite a lot of uncertainty in several parameters. The parameters with greatest influence on the result were the parameters included in the extrapolation, the relative risk of obesity-related diseases, the effectiveness of the intervention, the intervention cost and the incidence in diabetes. More evidence on the link between pre-school health behaviours and chronic diseases at adult age, and a lower intervention costs would have resulted in a better incremental cost-effectiveness ratio.

Conclusion: This health economic analysis has shown that the small health effects due to the ToyBox-intervention are not always in balance with the extra costs induced. The cost-effectiveness of such intervention programs is dependent on the effectiveness of the intervention, the link between pre-school health behaviours and chronic diseases at adult age, and the intervention cost. Future paediatric obesity prevention interventions should not only focus on the intervention effect but also on the induced costs. Besides, more evidence on the tracking of pre-school behaviour or weight to the adult age is desirable to reduce uncertainty.

INTRODUCTION

Over the last decades, sweets, sugar-sweetened beverages (SSB) and fatty snacks together with a passive lifestyle have nourished the increasing prevalence of overweight and obesity in pre-school children worldwide (Acosta et al., 2008; De Onis et al., 2010; Liebman et al., 2003). This trend not only has an impact on the health of children now and later in life (Acosta et al., 2008; Baker et al., 2007), but also negatively affects society due to higher health care costs and productivity loss (Konnopka et al., 2011; Kwaliteitsinstituut voor de gezondheidszorg CBO, 2008). With obesity being responsible for about 0.7% to 2.8% of a country's total health care expenditure (Withrow & Alter, 2011), the health and economic burden of paediatric obesity is substantial (Lobstein & Jackson-Leach, 2006). As most obesity-related health care costs are financed by the government, there is a strong motivation for policy makers to tackle the obesity epidemic. However, most of the health benefits of child obesity interventions do not emerge until adulthood, making health gains from the interventions difficult to observe, which impedes decisions to adopt such an intervention. Nonetheless, several obesity prevention programs for young children have been developed so far, with different designs and different outcomes (Laws et al., 2014; Pitangueira, Rodrigues Silva, & Costa, 2015; Waters et al., 2011). The ToyBox-study (short for 'Multifactorial evidence-based approach using behavioural models in understanding and promoting fun, healthy food, play and policy for the prevention of obesity in early childhood') aimed to develop, implement and evaluate a kindergarten-based, family-involved intervention to prevent obesity in early childhood (Manios, 2012). Modelling long term costs and benefits of the interventions is crucial, as to inform policy makers on the return on investment and to give advice on which interventions are worth implementing using public funding. In a previous publication, we informed on the design and data-inputs of the model to assess the cost-effectiveness of the ToyBox-intervention (Pil et al., 2014). In the current analysis, the cost-effectiveness of the ToyBox-intervention was evaluated by estimating the long term costs and effects in six European countries, namely Belgium, Bulgaria, Germany, Greece, Poland and Spain.

METHODS

The ToyBox-intervention

The ToyBox-intervention was a randomised cluster trial which was implemented within the academic year 2012–2013 in Belgium, Bulgaria, Germany, Greece, Poland and Spain. The intervention targeted four key health behaviours in pre-schoolers aged 3.5-5.5 years old, namely drinking behaviour, snacking behaviour, physical activity and sedentary behaviour (for the design and implementation of the ToyBox-intervention, see Manios et al. (2014)). By means of Repeated Measures Anova analyses, the ToyBox research group investigated the effects of the intervention on the anthropometric measures and key health behaviours of the pre-schoolers, based on a sample of 4,964 pre-schoolers (4.7±0.4 years; 51.5% boys) from the six included countries (unpublished work). After the implementation period, some significant, albeit modest, effects of the ToyBox-intervention in the total sample were found on total SSB

consumption (soft drinks, pre-packed fruit juices, and sugared milk) ($p < 0.001$) and on screen time (including time spent on watching TV, and/or playing computer- and video games) (borderline significant $p=0.06$). These variables were were defined in two categories <=1h/weekday versus >1h/weekday and <=65ml/day versus >65ml/day, based on the categories as used by De Coen et al. (2013) (cf. infra) (Table 1). The effect was slightly higher in SSB consumption than in screen time, but both effects were simulated together in the analyses. No effect was found on the anthropometric parameters, vegetable and fruit consumption, snacking behaviour or physical activity.

Table 1: Prevalence of pre-schoolers in the health behaviour categories

	Adjusted baseline measurement	**Post-measurement**	
		Intervention group	control group
Screen time			
<=1h/weekday	52.1%	52.2%	49.6%
>1h/weekday	47.9%	47.8%	50.4%
SSB consumption			
<= 65ml/day	35.8%	48.2%	40.5%
>65ml/day	64.2%	51.8%	59.5%

Model design

The health economic model developed for ToyBox was a combined model consisting of a decision analytic model to represent the probability of improved energy balance-related behaviours in children and the projection of this intervention effect to adult age (see Figure 1a in chapter 2.1.1.), followed by a Markov model (See Figure 1b in chapter 2.1.1.) simulating the occurrence of obesity-related complications in adults (from the age of 30) over a lifetime. The same model was used for the comparator, ignoring the intervention effect. Over a lifetime, the difference in costs between both alternatives was divided by the net effects (in Quality Adjusted Life Years - QALYs), to obtain the primary outcome measure, the incremental cost-effectiveness ratio (ICER). The ICER was interpreted assuming the gross domestic product (GDP) per capita of the country as willingness-to-pay threshold (WHO, 2005b). Since no literature was found to project the intervention effect on total SSB and screen time to adult obesity-related complications (i.e. the hard endpoints), an indirect calculation had to be made, through weight status (overweight/obese). First, based on a longitudinal study of De Coen et al. (2013), the intervention effect on screen time and total SSB at child age was projected to the child weight status two years later (mid-term). From the odds ratios they found in their study, we calculated the relative risk for screen time (categorised as >1h/weekday and ≤1h/weekday) to be 1.34 (95%CI 0.99 – 1.61), stating that pre-schoolers with 1 hour or more screen time per weekday are 34% more likely to be overweight/obese 2 years later in comparison to their peers with less than 1 hour screen time per weekday. Soft drink consumption (categorised as >65ml/day and ≤65ml/day) was associated with a

relative risk of 1.12 (95%CI: 0.89 – 1.31), stating that pre-schoolers with a soft drink consumption of >65ml/day are 12% more likely to be overweight/obese 2 years later in comparison to their peers with less than 65 millilitre soft drinks per day. Subsequently, this mid-term weight status of the children was extrapolated to adult weight status (at the age of 30) based on the relative risks calculated from the figures in the tracking study of Venn et al. (2007) (Table 2). This calculation was performed for the control as well as the intervention group. The estimated prevalence of overweight and obesity at adult age in case of the intervention was compared to the prevalence in the control group in order to calculate the relative risk reduction in overweight and obesity. Table 3 shows that, by means of the ToyBox intervention, which allows for a reduction in the number of children having more than 1 hour a day of screen time and a decrease in the number of children with more than 65ml SSB per day, it is expected that the prevalence of obesity in adult women relatively decreases with 2.07% (=0.91% + 1.16%). The association between adult weight status and obesity-related complications was obtained from the International Association for the Study of Obesity (2013) (Table 1, p.37 in this thesis). Finally, a risk reduction in the prevalence of overweight and obesity led to a risk reduction in the probability of obesity-related complications. More detailed information on the design of the cost-effectiveness model can be found in Pil et al. (2014). In order to gain information on the budget impact of the intervention cost, a cohort-analysis was performed simulating the impact of adding a new cohort each year over a period of 14 years (i.e. until the first cohort reaches the age of 18). Model validation is addressed in Appendix Table 1.

Epidemiological and health-economic model inputs

The prevalence of overweight and obesity in adults per country, was obtained by the Eurostat database (Eurostat, 2008a). Chronic disease incidences per country were obtained from the Globocan database (for cancer) (GLOBOCAN, 2012) and from published literature (Appendix Table 1, p.45-50 in this thesis). Costs were evaluated from a societal viewpoint, including direct health care costs related to the chronic disease states as well as indirect costs due to productivity loss, with reference year 2012 (Table 3, p.41 in this thesis). The cost of the intervention captured all costs that were incurred by the implementation of the intervention. The average intervention cost was €11.8 per pre-schooler, but was included country-specific in the model (see Table 2, p.39 in this thesis). QALYs were calculated using EQ-5D utilities, derived from literature data (Table 4, p.42 in this thesis). According to the Belgian guidelines, annual discount rates of 3.0% and 1.5% were applied to future costs and effects respectively (Cleemput et al., 2012). Details on the intervention cost assessment and QALY calculation are explained in Pil et al. (2014).

Table 2: Relative risks for the tracking of overweight and obesity into adulthood (from the age of 30), in reference to normal weight children

	Adult: Overweight		Adult: Obesity	
	males	*females*	*males*	*females*
Child 7-9y: Overweight	1.1	2.2	4.4	5.0
Child 7-9y: Obesity	1.1	0.9	5.0	9.8

Interpretation: e.g. a 7-9 year-old girl with overweight has a 5 times higher risk to become obese in adulthood in reference to a normal-weight 7-9 year old girl.
Source: calculated from the study of Venn et al. (2007). The figures specific for 7 to 9-year olds were obtained by personal communication with the authors.

Table 3: Relative risk reductions in adult overweight and obesity due to the ToyBox-intervention

	Screen time		Total SSB	
	males	*females*	*males*	*females*
Overweight	0.04%	0.23%	0.05%	0.30%
Obesity	0.73%	0.91%	0.93%	1.16%

Screen time: categorised as >1h/weekday and ≤1h/weekday
SSB: Sugar-sweetened beverages
Total SSB: categorised as >65ml/day and ≤65ml/day

Scenario- and sensitivity analysis

As the Toybox-study lacks a long term follow-up analysis, the duration of the intervention effect is unclear. There is however some evidence for the tracking of physical activity, sedentary behaviour and diet from childhood to adulthood (Busschaert et al., 2015; Craigie et al., 2011; Friedman et al., 2008), because of which one could argue that the change to the more healthy behaviour due to the intervention would sustain into adulthood. On the contrary, there is also evidence for a waning intervention effect over time (Hoffman et al., 2011; Wen et al., 2015). Therefore, in order to sustain the original ToyBox-intervention effect, we assumed a Toybox-similar intervention to be repeated annually in the base case model until the age of 18. Some scenarios concerning the intervention effect were explored for the Belgian case. A first scenario included a biennial implementation of a ToyBox-similar intervention instead of annually, assuming the intervention-effect to last for 2 years. In a second scenario the annual repetition of an intervention to sustain the effect of the ToyBox-intervention until the age of 30 instead of 18 was included.

One-way- and probabilistic sensitivity analyses were conducted to capture uncertainty in the key parameters and to assess the effect of variation in the parameters on the ICER. In the one-way sensitivity analysis the individual effect of the intervention cost, total costs per disease state, the intervention effect, the relative risk of screen time and total SSB related to mid-term weight status, the relative risk of tracking for overweight and for obesity from childhood to adulthood, the relative risk of adult overweight and obesity on obesity-related diseases, disease incidences and the utilities per disease state was evaluated in case of better or worse conditions of these parameters -defined by the confidence interval or ±30% variation in case confidence intervals were absent. A probabilistic analysis varied the costs, utilities, disease incidences and the relative risks concurrently by their own probability distribution. Cost data were assumed to be distributed according to a gamma-distribution, utilities and

incidences according to a beta-distribution and the relative risks according to a log-normal distribution (Briggs et al., 2006).

RESULTS

Results were expressed over a period of 70 years, per 1,000 pre-schoolers per country, and for males and females separately (Table 4). Assuming the GDP per capita of the country as willingness-to-pay threshold (WHO, 2005b), the ToyBox-intervention, leading to less screen time during weekdays and less consumption of total SSB, was cost-effective in Spain and in Poland, the latter only in females. ICERS were €19,893/QALY and €9,094/QALY in Spanish males and females respectively and €5,758/QALY in Polish females. In Belgian and Greek females, the analysis showed a borderline cost-effective result. In the other countries, the incremental cost-effectiveness ratio was above the assumed threshold. Although the intervention effect was assessed for the total sample, not separated according to gender, in all countries the result was better in females than in males. The worse cost-effectiveness results (in reference to the particular threshold) were found in Bulgaria and Germany.

The scenario-analysis showed that a longer duration in the intervention effect, which would lead to the intervention being re-implemented biennially instead of annually, would decrease the (intervention) costs, while the health effects remain equal. Therefore, this would be a more cost-effective scenario (Table 5, results shown for Belgium), with an ICER below the threshold in females as well as males. If the intervention would have to be repeated until the age of 30 in order to sustain a stable effect throughout life, the intervention cost would increase and the result would be worse compared to the base case. One-way sensitivity analyses showed the most influential parameters, for the result in all countries, to be the relative risk of SSB and screen time on the mid-term weight status, the relative risk of obesity on obesity-related diseases, the cost of the intervention, the relative risk related to the tracking of overweight/obesity, the incidence of diabetes and the ToyBox-intervention effect on total SSB and screen time (see tornado diagrams in Figure 1, shown for the Belgian analysis). An increase in the value of these parameters resulted in a better cost-effectiveness result, except for the cost of the intervention, in which there was an opposite effect. Second order Monte Carlo analyses were performed to assess the effect of the uncertainty associated with the key parameters simultaneously. The probabilistic sensitivity analyses created credibility intervals around the mean estimate, which are shown in Table 4. The cost-effectiveness planes (Figure 2, shown for Belgium) display the simulated cost- and QALY-points which are all situated in the north-east and north-west quadrants of the plane. The cost-effectiveness acceptability curves depict the probability of the result being cost-effective considering different willingness-to-pay threshold (Figure 3, shown for females). The highest probabilities were found in the analysis for Poland and the lowest in the analysis for Germany. The probability of the result in each country being cost-effective considering the GDP as the threshold is shown in Table 4. These probabilities were highest for Spain, Belgium and Poland, and lowest for Bulgaria and Germany.

Simulating the intervention cost for all Belgian pre-schoolers, until the original cohort of children reaches the age of 18 (i.e. for a period of 14 years on average), while every year a new cohort of 3 years-old

enters the model, would result in a total intervention cost of €105,031,189 million for the Belgian public payer. This equals €3 per year per child from the target group (3-6 year-olds, including annual inflow of new 3 year-olds). This is a maximum scenario, assuming a 100% participation rate to the program.

Table 4: results of the cost-effectiveness analysis, expressed per 1,000 persons.

	GDP per capita (2012)*	Δ Costs		Δ QALYs		ICER deterministic		ICER probabilistic mean (95% CI)		Cost-effectiveness probability	
		males	*females*	*males*	*females*	*males*	*females*	*males*	*females*	*males*	*females*
Belgium	€ 34,400	€ 117,355	€ 113,209	2.2	3.1	€ 52,847	€ 36,304	€ 54,103 (€16,880 - €372,878)	€ 37,422 (€12,357 - €234,296)	16.8%	43.2%
Bulgaria	€ 5,650	€ 64,324	€ 58,951	1.7	3.8	€ 38,194	€ 15,527	€ 38,779 (€13,769 - €238,372)	€ 16,087 (€5,535 - €110,784)	0.0%	1.0%
Germany	€ 33,900	€ 298,772	€ 287,874	3.6	5.1	€ 82,480	€ 55,974	€ 83,843 (€29,708 - €542,242)	€ 57,432 (€17,676 - €446,917)	1.9%	14.3%
Greece	€ 17,100	€ 107,238	€ 97,388	3.2	5.1	€ 33,298	€ 19,417	€ 33,771 (€11,138 - €226,433)	€ 20,279 (€5,663 - €140,325)	7.3%	37.3%
Poland	€ 10,100	€ 53,517	€ 42,143	2.8	7.3	€ 19,215	€ 5,758	€ 19,991 (€-11,287 - €145,332)	€ 6,304 (€1,277- €44,637)	9.4%	72.5%
Spain	€ 22,000	€ 72,551	€ 57,457	3.7	6.3	€ 19,893	€ 9,094	€ 21,719 (€2,646 - €178,296)	€ 10,568 (€476 - €87,298)	84.9%	78.4%

Δ: incremental; QALYs: Quality-adjusted life-years; * (Council of the European Union, 2010)

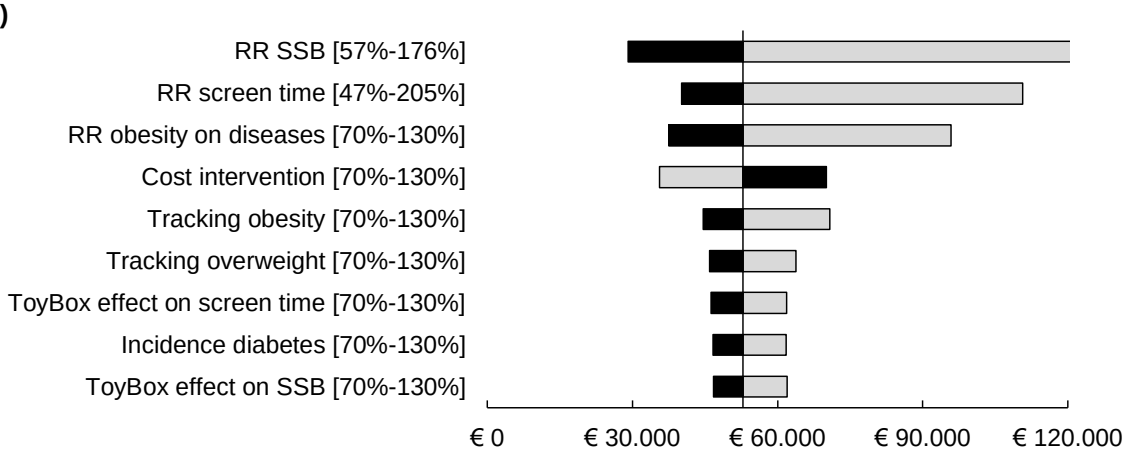
Table 5: Results from scenario analysis for Belgium, expressed per 1,000 persons.

	Δ Costs		Δ QALYs		ICER	
	males	*females*	*males*	*females*	*males*	*females*
Base case	€ 117,355	€ 113,209	2.2	3.1	€ 52,847	€ 36,304
Similar intervention biennially	€ 54,336	€ 50,191	2.2	3.1	€ 24,469	€ 16,095
Similar intervention annually until 30y	€ 181,221	€ 177,075	2.2	3.1	€ 81,607	€ 56,785

Δ: incremental; QALYs: Quality-adjusted life-years

Figure 1: Tornado diagrams for the one-way sensitivity analysis in males (A) and females (B), Belgium

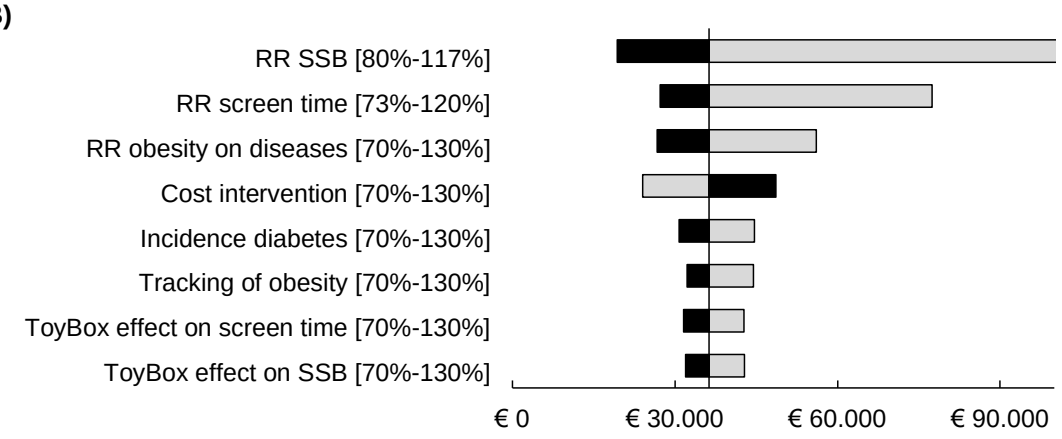
A)



RR: relative risk; SSB: sugar-sweetened beverages

Light-coloured bars show the result in case of a minimum value on the parameter, dark-coloured bars show the result in case of a maximum value on the parameter.

B)



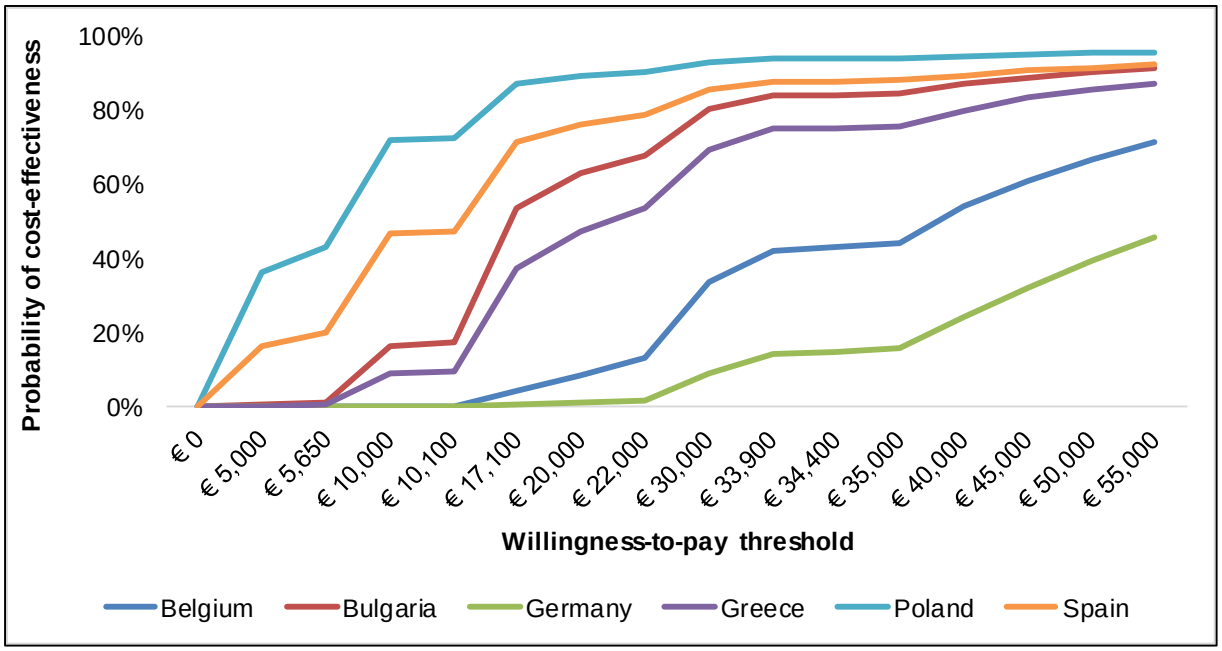
RR: relative risk; SSB: sugar-sweetened beverages

Light-coloured bars show the result in case of a minimum value on the parameter, dark-coloured bars show the result in case of a maximum value on the parameter.

Figure 2: Cost-effectiveness planes for the analysis in Belgian males (A) and females (B), expressed per 1,000 persons

Black line through the cloud = willingness-to-pay threshold

Figure 3: cost-effectiveness acceptability curve



DISCUSSION AND CONCLUSION

This article described the results of the cost-effectiveness analysis of the ToyBox-intervention for the six participating countries. The ToyBox-intervention resulted in modest effects on the total SSB consumption and screen time of the pre-schoolers. Consequently, this cost-effectiveness analysis showed only a minimal gain in QALYs per person, in all six countries. However, when this QALY-gain would apply to the total target population of pre-schoolers, a potentially large public health benefit could be achieved. However, in most of the analyses, the health benefit did not compensate for the extra costs related to the intervention. The probability of the intervention being cost-effective was the lowest in Bulgaria and Germany. This has probably to do with the intervention cost (which was high in Germany (Pil et al., 2014)), but also with assumed the willingness-to-pay threshold (which was very low in Bulgaria). The result for the Bulgarian analysis had the lowest probability of being cost-effective

considering the GDP per capita of the country as the threshold. However, Figure 4 shows that in case the threshold for Bulgaria would have been higher, the probability would not have been the lowest of all countries. Besides, results were better in females than in males, mainly because tracking of obesity from childhood into adulthood is stronger in females (Venn et al., 2007), which results in the relative risk reduction in overweight and obesity due to the intervention effect being larger in females. The analysis for Spain and for Polish females resulted in a good ICER, probably due to modest intervention cost and for Spain also because of the incidence of diabetes being quite high (compared to the other included countries). The value of these two parameters varied between the included countries and it was shown that uncertainty in these parameters had a high impact on the cost-effectiveness result.

The intervention effect on the pre-schoolers' EBRBs was extrapolated to the adult age since chronic diseases generally start to develop at adult age. Similar extrapolations from childhood to adulthood have been performed previously in cost-effectiveness analyses of childhood obesity programs (Brown et al., 2007). Some intermediate extrapolations had to be made in our analysis, as no current literature describes the relation between child health behaviours and risk on chronic diseases in adulthood. However, such a causal chain induces extra uncertainty in the model, which needs to be explored in sensitivity analyses. The cost-effectiveness result was influenced by all included parameters in the model of which the most influential were the relative risks included in the causal chain (Figure 1a, chapter 2.1.1.), the intervention cost and -effect and the incidence of diabetes. It is clear that a stronger relation between the EBRB at child age and the weight status at mid-term, would have resulted in better ICERs. This argues for more research on the relation between child health behaviour and weight status, or even better, between child health behaviour and adult weight status or adults risk on obesity-related diseases. Additionally, it was shown that when the intervention effect would sustain for 2 years, the cost-effectiveness results would be better. This observation shows the importance of having more information on the duration of the intervention effects of the ToyBox-intervention, but also of similar interventions in general, in order to simulate the long term effects of such prevention interventions.

Other cost-effectiveness analyses of obesity prevention interventions in children included for example the evaluation of an early childhood home visiting program in Sydney (Hayes et al., 2014), an after-school program designed to prevent obesity among elementary school students (Wang et al., 2008) and a multicomponent through-school physical activity and nutrition program, delivered to all primary school children in a New Zealand region (Moodie, Carter, Swinburn, & Haby, 2010), which were all found to be cost-effective. In contrast, Moodie et al. (2011) evaluated an active transport program for primary school children and found that this intervention was not cost-effective. However, these interventions targeted primary school children instead of pre-schoolers and did not include long term costs and health effects. Our study assessed the impact on the long term costs and health effects of an international kindergarten-based, family-involved intervention of obesity prevention in European pre-schoolers and therefore has added value to the previous published literature.

Notwithstanding the value of our study, some limitations need to be addressed. First, in order to be able to use the relative risks assessed by De Coen et al., weight was included as the body mass index-categories overweight and obesity. Adverse health consequences are positively correlated with the

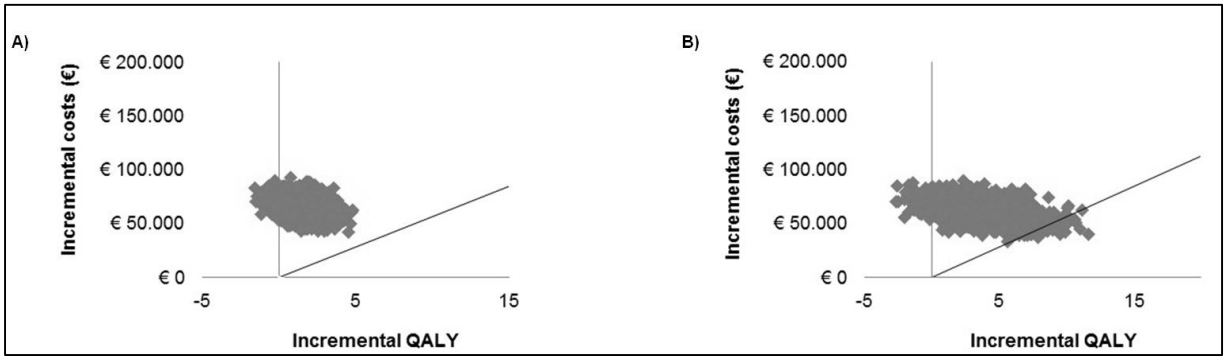
severity of obesity (WHO, 2000), which leads to differences in quality of life among those experiencing different obesity severity. In our model, by using weight status categories, it was not possible to account for differences in the severity of obesity. Second, De Coen et al. found an effect of screen time and soft drink consumption on mid-term overweight/obesity. The effect on soft drink consumption was applied to total sugared-beverage consumption in our model, including not only soft drinks, but also pre-packed fruit juices and sugared milk. Moreover, there was only a trend in significance in the risks measured by De Coen et al., although we took the uncertainty in these parameters into account in the probabilistic sensitivity analysis. Third, it is possible that the ToyBox-intervention led to other health effects which were not captured in the effectiveness and cost-effectiveness analysis, such as change in parental health behaviours, empowerment, social contact, etc. Fourth, we did not perform sub-group analyses according to socio-economic status (SES) to account for variation in the cost-effectiveness of the intervention. It is possible that the intervention had another effect in pre-schoolers with a lower SES, resulting in different cost-effectiveness ratios between high- and low SES children. Additionally, published literature describes differences in the epidemiology of obesity-related disease according to SES, which could have an impact on the results (Fiscella & Tancredi, 2008; Manser & Bauerfeind, 2014; Marshall et al., 2015; Orsini, Tretarre, Daures, & Bessaoud, 2016; Rabi et al., 2006). Finally, it should be noted that the results could not be directly compared between the countries, as they are to be interpreted based on the assumed country-specific willingness-to-pay threshold.

To conclude, the ToyBox-intervention was found to be only cost-effective in case of a modest intervention cost, a high incidence of diabetes and a beneficial willingness-to-pay threshold. Future interventions should bear in mind that intervention costs should be as low as possible, while maintaining a high effectiveness. Additionally, more research is necessary on the long term duration of the effect of prevention interventions and on the relation of pre-schooler health and later morbidity.

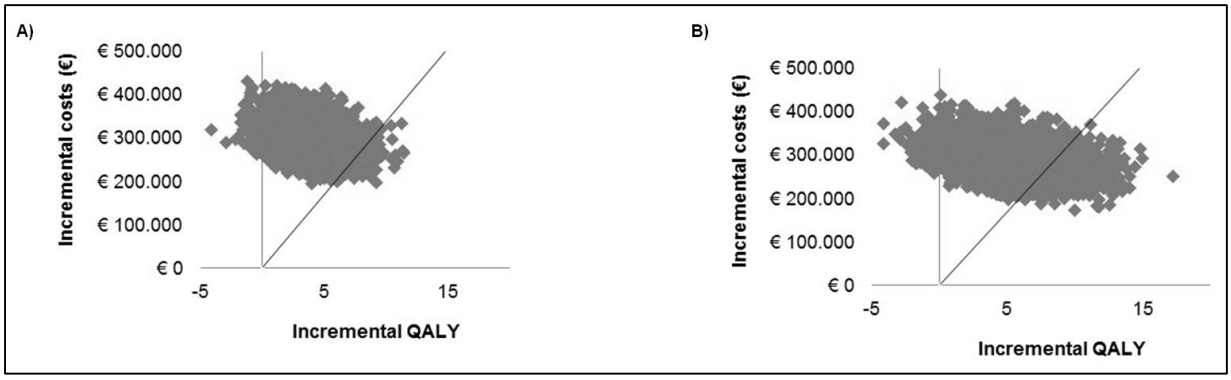
APPENDIX

Appendix Figure 1: Cost-effectiveness planes for the analysis in males (A) and females (B)
(costs and QALYs expressed per 1,000 persons)

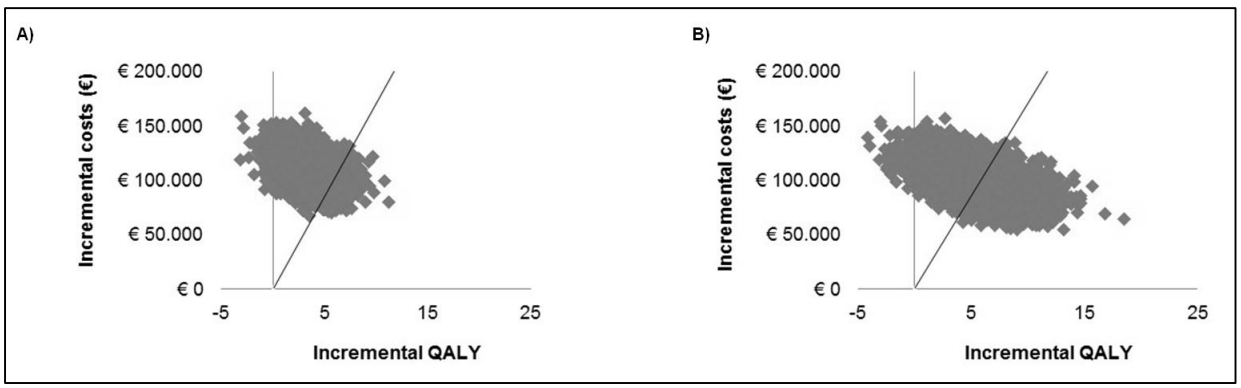
Bulgaria



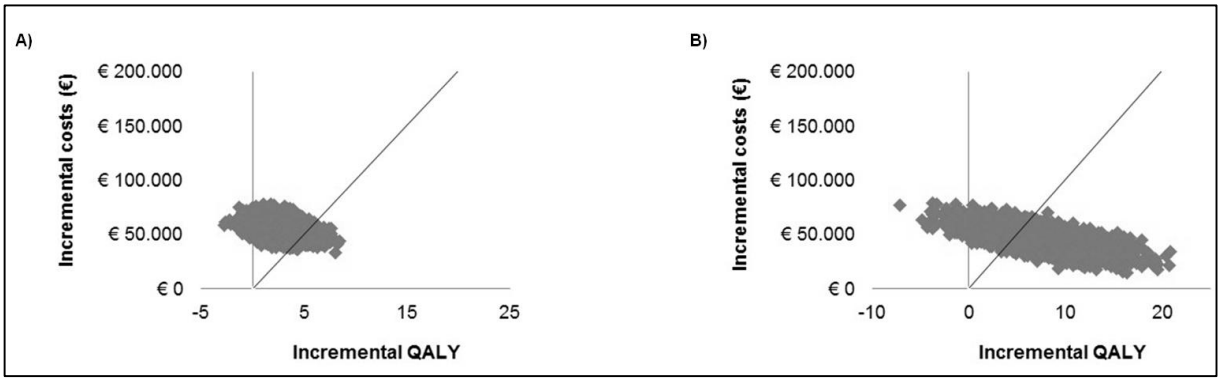
Germany



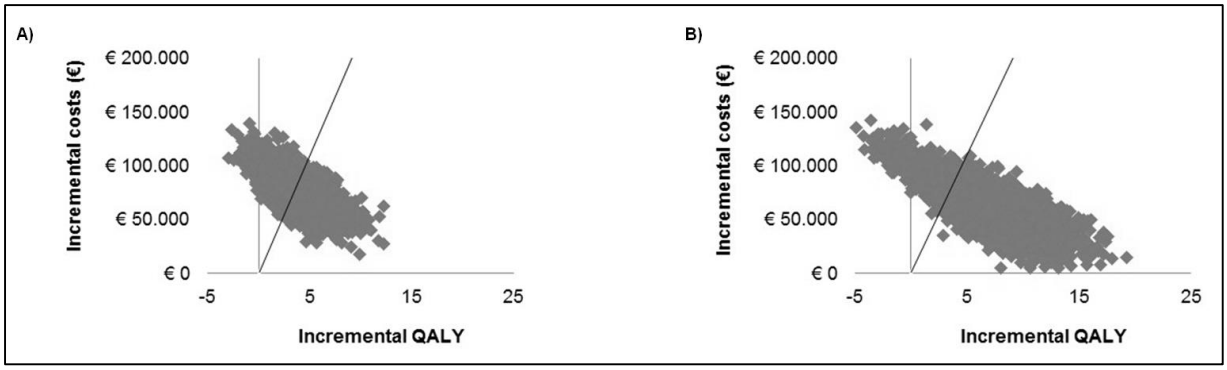
Greece



Poland



Spain



Appendix Table 1: Model validation: average 1y predicted versus observed prevalence in the Belgian adult population

	Diabetes[a]	Colorectal cancer[b]	Breast cancer[b]	Stroke[a]	Coronary hearth disease[a]
females					
model	5.1%	0.4%	1.4%	1.4%	1.2%
observed	**5.9%**	**0.5%**	**2.4%**	**1.3%**	**1.9%**
males					
model	3.4%	0.3%		2.1%	3.0%
observed	**6.0%**	**0.5%**		**1.4%**	**2.8%**

a: 1y prevalence based on Health Interview Survey, 2008-2013 (Scientific Institute of Public Health., 2013)

b: 1y prevalence based on the Belgian Cancer Registry, 2010 (Belgian Cancer Registry, 2010a; Belgian Cancer Registry, 2010b)

Explanation Appendix Table 1:

In order to validate the outcomes of the model for the Belgian analysis, the predicted average 1y-prevalence of obesity-related diseases over 70 years in the control arm was compared with the observed 1y-prevalence, based on Belgian data. The prevalence of diabetes (especially in males), colorectal and

breast cancer was slightly underestimated in the model. The prevalence of stroke and coronary heart disease (in males), was slightly overestimated. Despite the differences, the predicted data seems to approximate observed prevalence data.

2.1.3. Burden of skin cancer in Belgium and the cost-effectiveness of prevention by reducing ultraviolet exposure

Based on:

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ABSTRACT

Background: Skin cancer (melanoma- and non-melanoma skin cancer) is one of the most rapidly increasing cancers worldwide.

Objective: This study analysed the current and future economic burden of skin cancer in Belgium and the cost-effectiveness of two strategies in the prevention of skin cancer by reducing ultraviolet exposure.

Methods: A retrospective bottom-up cost-of-illness study was performed, together with a Markov model in order to analyse the cost-effectiveness and the budget impact analysis of a comprehensive sensitisation campaign and a total ban on sunbeds in Belgium.

Results: Total prevalence of skin cancer in Belgium was estimated to triple in the next 20 years. The total economic burden of skin cancer in 2014 in Belgium was estimated at €107 million, with a cumulative cost of €3 billion in 2034. The majority of this total cost was due to melanoma (65%). Over a period of 50 years, both prevention programs would lead to a gain in quality-adjusted life-years (sensitisation campaign: 1.39 QALY per 1,000 males and females; ban on sunbed use: 4.81 and 5.94 QALY per 1,000 males and females respectively) and cost-savings (sensitisation campaign: €15,273 and €17,411 per 1,000 males and females respectively; ban on sunbed use: €19,886 and €20,384 per 1,000 males and females respectively). For every euro invested in the campaign, €3.6 would be saved on the long term for the health care payer.

Conclusion: Policy makers and clinicians should promote ultraviolet protection strategies, as these are estimated to be dominant strategies.

INTRODUCTION

Skin cancer is increasing globally (Arits, Schlangen, Nelemans, & Kelleners-Smeets, 2011; Flohil et al., 2013a; Flohil, De Vries, Neumann, Coebergh, & Nijsten, 2011; Nikolaou & Stratigos, 2014), and affects nearly one out of five persons in Belgium. It is related to ultraviolet exposure, either naturally from the sun or artificially through solarium use. These risk factors are the strongest for non-melanoma skin cancer (NMSC) - defined as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) -, however meta-analyses also confirm the influence in development of melanoma skin cancer (MSC) (Boniol, Autier, Boyle, & Gandini, 2012; Elwood & Jopson, 1997). Several epidemiologic studies show an alarming global increase in the incidence of MSC and NMSC, due to the increasing age of the population, but also to altered risk seeking behaviour (De Vries, Van de Poll-Franse, Louwman, de Gruijl, & Coebergh, 2005; Diffey, 2004; Flohil et al., 2011; Hollestein, De Vries, & Nijsten, 2012; Marcos-Gragera et al., 2010). Although NMSC is less aggressive than MSC, it has an important impact on the health expenditures because of the high prevalence (Stang, Stausberg, Boedeker, Kerek-Bodden, & Jockel, 2008). Consequently to this epidemic, the related health care costs are rising significantly. Current opinion in Europe states that the rise in health care spending is not sustainable in the future, so studies with a focus on estimating current expenditures on skin cancer and innovative ways to improve cost-effective health care and prevention are needed. However, despite the growing awareness of the magnitude of the skin cancer burden, such studies on this subject are scarce. Besides, currently, most studies on universal prevention focus on MSC or are performed in a high prevalent setting such as Australia (Gordon et al., 2009; Hirst, Gordon, Scuffham, & Green, 2012; Hirst, Gordon, Gies, & Green, 2009; Shih, Carter, Sinclair, Mihalopoulos, & Vos, 2009). For this reason the first objective of this study was to calculate the current and future health and economic burden of MSC and NMSC in Belgium. Estimating the total cost of skin cancer is particularly useful for measuring the potential cost savings from averting new skin cancer cases, emphasising the importance of skin cancer prevention. As such, this study also simulated the cost-effectiveness and budget impact of a hypothetical sensitisation campaign and a hypothetical total ban on sunbed use.

METHODS

Burden of skin cancer

The health-related burden of skin cancer was estimated based on the registered prevalence of skin cancer lesions being in treatment, in intense follow-up or in long-term follow-up. (Belgian Cancer Registry, 2013; Integraal Kankercentrum Nederland, 2011). This current prevalence was projected to 2034, taking into account the ageing of the population (since the cohort ages each cycle) and other skin-cancer related trends such as going on holiday more often or getting a check-up more frequently, based on the estimated annual increase of skin cancer incidence (Flohil et al., 2013a; Hollestein et al., 2012; Hollestein et al., 2012). In order to estimate the total economic burden of skin cancer on society, a bottom-up cost-of-illness study was conducted, based on retrospective information from Belgian patient questionnaires being gathered from 1st March 2015 until 30th June 2015. Dermatologists and oncologists working in general and university hospitals, small (< 200 beds), medium (200-400 beds) or

big (> 400 beds) hospitals, as well as private practices were recruited in December 2014. These physicians were asked to give skin cancer patients the information about the study and to hand out the questionnaires to the patients. Eligible patients were those who were 18+, had a diagnosis of MSC, BCC and SCC maximum ten years ago and who presented to a participating physician between 1st March 2015 and 30th June 2015. Patients were asked questions about their medical consumption for their skin disease during the last six months, as well as about their productivity loss and quality of life. Questions concerned the number of consultations, number and type of examinations, drug use, number of days absent from work and health-related quality of life (based on the EQ-5D-5L questionnaire). Ethics committee approval and patient informed consents were obtained. Based on the resource utilisation patterns for individuals with MSC, BCC or SCC and official Belgian unit costs (Rijksinsituut voor Ziekte- en Invaliditeitsverzekering (RIZIV), 2016), we calculated the cost per skin cancer stage per six months, separately for diagnosis and treatment, intense follow-up and long term follow-up. The current total societal cost was calculated by multiplying these direct costs per cancer stage with the prevalence of detected skin cancer (defined as patients in treatment as well as patients in follow-up) and by multiplying the cost per day absenteeism (Cleemput et al., 2012) with the number of days absent from work due to skin cancer (based on the patient questionnaires). In order to calculate the future cost of skin cancer in Belgium, a Markov model was composed (Microsoft Excel® 2013), with a time horizon of 20 years. All costs were computed at the 2014 euro price level and expressed separately as costs for the public health care payer, costs for the patient (co-payment) and costs due to productivity loss.

Health economic evaluation of two universal prevention strategies

A Markov state-transition cohort model was developed, examining the economic impact and the cost-effectiveness of a hypothetical sensitising prevention campaign and a hypothetical total ban on sunbed use in reference to the current situation. A Markov model is a type of decision model based on a series of states that a person can occupy at a given point in time (Drummond et al., 2015). MSC as well as NMSC were included in the model, consisting of different disease states: undiagnosed skin cancer, diagnosis & treatment, follow-up and death (Appendix Figure 1), separated per skin cancer stage. The duration of the diagnosis & treatment phase was 6 months (= 1 cycle) for patients with BCC, SCC 0-II or MSC I-II and 1 year for patients with SSC III-IV or MSC III-IV. To assign a higher probability of skin cancer death in the first years after diagnosis in case of SCC IV and MSC IV, the follow-up phase was divided into intense- and long term follow-up, which lasted for 4 years, after which one moved into long term follow-up. Patients in follow-up remained in this state until the end of the model's time horizon, or until they died. MSC and SCC stages were determined according to the 7th edition of the Tumour-Nodes-Metastases-classification for malignant tumours (Sobin, Gospodarowicz, & Wittekind, 2009). Stages for BCC were defined as <1cm, 1-2cm, >2cm and aggressive histology. BCC and SCC patients were assigned a higher risk to develop an MSC lesion. All cohort members started the model in one of the model states, according to the baseline prevalence of BCC, SCC and MSC (Belgian Cancer Registry, 2013; Integraal Kankercentrum Nederland, 2011). Transitions between the disease states were possible every six months. Health effects and costs of a cohort of Belgian adult males and females were simulated from a societal perspective, during a time horizon of 50 years. This time horizon included an

induction period (i.e. the period between risk factor exposure – being UV exposure – and the onset of skin cancer) of 20 years (based on expert opinion), and therefore had to be long enough in order to capture all relevant effects. Main outcomes included the incremental cost-effectiveness ratio (ICER), the total economic societal impact as well as the impact on the health care budget, and the estimated reduction in skin cancer incidence and mortality. The ICER was calculated by dividing the net costs by the net health benefits of the prevention program in reference to the current approach (i.e. absence of such a program). The budget impact analysis estimated the net cumulative cost of both prevention programs (and consequent examinations, treatment and follow-up) for the public health care payer over a period of 20 years. In order to calculate the societal economic burden and the health care budget impact, the model allowed each cycle new entrance of 18-year olds in the lesion-free state, who were subjected to the natural skin cancer progression.

Intervention strategies

1) Sensitisation campaign reducing risk of sunburn

The hypothetical sensitisation campaign was defined as a comprehensive program such as the SunSmart campaign in Australia. SunSmart is a public education program which has been running in Australia (especially in the state Victoria) since 1987 (Hill et al., 1993). In the first implementation years, the major SunSmart communication strategy was a mass media campaign to raise awareness, to model preventive behaviour and to present 'SunSmart'-behaviour as fashionable (Hill et al., 1993).

The impact of a hypothetical comprehensive sensitisation campaign on skin cancer was modelled through an effect on being sunburned. Sunburn is an indicator of acute high sun exposure but no dose response for the number of sunburns leading to MSC has been clearly established (Shih et al., 2009). Published literature has shown the impact of ever being sunburned on the risk of MSC to be preventable by means of comprehensive prevention campaigns. Hill et al. (1993) evaluated the SunSmart campaign in Australia two years after its implementation and found an effect on reducing sunburns by 41% (RR 0.59). The risk on developing MSC was estimated to be 59% higher for persons ever being sunburned during lifetime in reference to those never being sunburned (RR 1.59, 95%CI (1.37-1.83); Table 1) (Dennis et al., 2008). No evidence was found for the impact of sunburns on SCC (Veierod, Couto, Lund, Adami, & Weiderpass, 2014) or BCC. As there is no evidence on the duration of the effect, in our analysis the prevention campaign was implemented annually.

2) Ban on sunbed use

In this analysis, the hypothetical ban on public sunbed use was defined as a total ban. Boniol et al. (2012) found in their meta-analysis –based on 18 cohort studies- a relative risk of MSC of 1.25 (95%CI: 1.09-1.43) for people who have ever versus those who have never used sunbeds (Table 1). The relative risk of SCC was 1.93 (Veierod et al., 2014) and for BCC no evidence on excess risk was found (Hirst et al., 2009; International Agency for Research on Cancer, 2007).

3) Comparator

The comparator intervention is the current situation, namely without such a sensitisation campaign and without a total ban on sunbed use. As our cost-effectiveness analysis is an incremental analysis, it is assumed that only the extra costs of the strategies evaluated are considered in the analysis. It is assumed that the current local fragmented initiatives would still exist in case of a national sensitisation campaign.

Table 1: input parameters related to the impact of the prevention strategies on health

Parameter	Mean (SE)
Prevalence of ever sunburned; Belgium[a]	90%
RR of sunburn if campaign[b]	0.59 (0.11)
RR of skin cancer if ever sunburned	
MSC[c]	1.59 (0.12)
SCC[d]	1
BCC	1
Prevalence of ever used sunbed; Belgium[e]	47%
RR of skin cancer if ever used sunbed	
MSC[f]	1.25 (0.09)
SCC[d]	1.93 (0.43)
BCC[g]	1

RR: Relative risk

a Expert opinion; b (Hill et al., 1993); c (Dennis et al., 2008); d (Veierod et al., 2014); e (Ipsos Public Affairs, 2013); f (Boniol et al., 2012); g (Hirst et al., 2009)

Input data

Prevalence of diagnosed MSC was derived from the Belgian Cancer Registry (2013) and of NMSC from the Dutch cancer registry (Integraal Kankercentrum Nederland, 2012a), since NMSC is more accurately registered in the Netherlands. A correction factor was applied to adapt the NMSC figures to Belgium, based on the ratio between the MSC mortality of both countries (factor: 0.51). Prevalence of undiagnosed skin cancer was derived from a previously organised screening trial including a Total Body Examination (TBE) and a Lesion-Directed screening (Hoorens et al., 2016) (see Chapter 2.2.3 for more information). Information on the probability of natural progression can be found in the appendix. Risk of recurrence in a treated lesion was accounted for in the model and risk of developing a subsequent lesion was included in the costs (Flohil et al., 2013b; Francken et al., 2008; Frost, Williams, & Green, 2000; Gandini et al., 2005; Leiter et al., 2012; Pomerantz, Huang, & Weinstock, 2015; Rees et al., 2014; Rowe, Carroll, & Day, Jr., 1992). The probability of spontaneous clinical detection was defined as the average prevalence of diagnosed skin cancer divided by the total prevalence (diagnosed and undiagnosed). All-cause mortality risk was applied to all persons in the model (based on Belgian life tables), whereas

mortality from skin cancer was applied only to patients with MSC or SCC stage III or IV (Belgian Cancer Registry, 2014). All epidemiologic and clinical input data are depicted in Appendix Table 1. The study was performed from the societal perspective, including direct medical costs as well as costs related to productivity loss because of morbidity and early mortality. Travel costs of patients were not included. Direct costs were identified as those medical health care resources consumed due to detection, diagnosis, treatment and follow-up, obtained from the 287 completed patient questionnaires. Indirect costs reflect the cost of absenteeism due to the management of the skin cancer. The cost for the sensitisation campaign was based the study of Shih et al. (2009) who estimated the annual future cost for the SunSmart intervention to be €0.17 per capita. Applied to the Belgian population, this would imply a total cost for the campaign of €1,525,998 per year. The possible associated costs of implementing a sunbed ban and financial consequences for the industry were not taken into account. Health effects of the universal prevention programs were defined as the impact on quality-adjusted life-years (QALYs) and skin-cancer related deaths. Stage-specific QALYs were based on the EuroQol 5 dimensions questionnaire (EQ-5D). The EQ-5D was included in the patient questionnaires, from which utilities were derived in combination with literature data (extra information and table in Appendix). Following Belgian guidelines, health effects were discounted at 1.5% and costs at 3% (Cleemput et al., 2012).

Scenario and sensitivity analysis

In the base case scenario an induction period of 20 years was assumed. However, since the duration of this period is not well documented, we varied it between 10 and 30 years. A second scenario consisted of the implementation of the combination of both a sensitisation campaign and a ban on public sunbed use. A one-way sensitivity analysis assessed the impact of variation in the key parameters one by one (according to the confidence interval (CI), or relative variation of ±30% in case no CI was available) in order to take into account uncertainty in the input variables. These parameters were the natural progression of skin cancer, prevalence and incidence data, effectiveness measures of the intervention strategies, disease-specific mortality, cost of the intervention, direct and indirect costs, utilities and the discount rate. A probabilistic sensitivity analysis (PSA) created credibility intervals around the deterministic ICER by running 5,000 (Monte Carlo) simulations according to the distribution of the parameters. Utilities and probabilities were varied according to beta-distributions, costs according to a gamma-distribution and relative risks according to a lognormal distribution (Briggs et al., 2006).

RESULTS

Burden of skin cancer

Sample characteristics

In total 16 dermatologists, nine oncologists and one general practitioner, employed in 10 different hospitals and six private practices participated in the study. In total, we received 287 completed patient questionnaires in a time span of four months. Response rates were 82.8% in dermatology patients and 71.9% in oncology patients. The sample consisted of 56% women and 44% men. The median age-category was 61-70 years old. Table 2 displays the stage distribution per cancer type.

Table 2: Distribution of study population according to skin cancer type and stage (N)

	D&T	*Intense FU*	*Long term FU*	*Total*
BCC <1cm	19	17	15	*51*
BCC 1-2cm	26	10	3	*39*
BCC>2cm	8	1	0	*9*
BCC aggressive hist.	6	4	3	*13*
SCC 0-I-II	7	11	10	*28*
SCC III	0	2	0	*2*
SCC IV	0	0	0	*0*
MSC 0-I	15	43	42	*100*
MSC II	5	7	3	*15*
MSC III	8	8	3	*19*
MSC IV	2	8	1	*11*
Total	***96***	***111***	***80***	***287***

D&T: Diagnosis and treatment; hist.: histology; FU: follow-up

Duration D&T:	*BCC, SCC 0-II, MSC I-II: 6 months (1 cycle)*
	SSC III-IV, MSC III-IV: 1 years (2 cycles)
Duration intense FU:	*BCC, SCC 0-II, MSC I-II: 1.5 year (3 cycles)*
	SSC III-IV, MSC III-IV: 4 year (8 cycles)
Duration long term FU:	*lifetime*

Epidemiology of skin cancer

The model estimated the total number of skin cancers in 2014 in Belgium to be 137,117, of which the greatest part (70%) were BCC cases (males: 45,480; females: 50,390), 18.5% were SCC cases (males: 12,278; females 13,066) and 11.5% were MSC cases (males: 6,239; females: 9,663). There were more female than male skin cancer patients, with a ratio of 1.13 to 1. This current prevalence is estimated to have tripled by 2034, to 397,213 skin cancer cases, of which 66% BCC (males: 101,932; females: 160,221), 21.2% SCC (males: 39,280; females: 45,114) and 12.8% MSC (males: 16,706; and females 33,960). The ratio of increase for MSC, SCC and BCC was respectively 3.2, 3.3 and 2.7.

Cost of skin cancer and the potential impact of prevention

For some patient groups (i.e. all stages of SCC and the more severe lesions of MSC) the response rate was low. To increase the power of the study, the direct cost was calculated based on guidelines produced by the European Dermatology forum (Euroderm) as well as dermatologist and oncologist expert opinions. For these groups with low sample, a care pathway was constructed that reflected current management patterns as accurate as possible. Also for large and aggressive BCCs, there was a low response rate. Therefore, the cost related to larger and aggressive BCCs was calculated from the cost related to a small BCC (<1cm) based on the ratios reported by Rogers & Coldiron (2009). Table 3 shows the cost per skin cancer stage, expressed per six months. As already stated in previously published studies (Alexandrescu, 2009; Tromme, 2015), it is clear from the table that costs increase with tumour stage. There were almost no costs due to productivity loss in NMSC patients. The total

economic burden of skin cancer on society in 2014 in Belgium was estimated at €107 million, with direct costs being €78 million and indirect costs being €29 million (Table 4). The majority of this total cost was due to MSC (65%). Costs were slightly higher for females than for males. Costs due to productivity loss were ten times higher in MSC patients than in NMSC patients, whereas costs for the patient were higher in case of NMSC. The total discounted cost in 2034 amounted to €142 million; the total cumulative cost over a period of 20 years (up to 2034) was estimated at €3 billion and over 50 years €8 billion. The Markov model simulation over 50 years showed that of the total cumulative societal burden (including direct and indirect costs) of €8 billion, €228 million could be saved by a sensitisation campaign and €238 million by a total ban on sunbeds, which is respectively 2.8% and 2.9% of the total societal burden (Table 5). The budget impact analysis demonstrated that a campaign could save €142 million for the health care budget (i.e. about 0.35% of the current public health care budget), initial investment cost taken into account, and in case of a ban on sunbed use €167 million (i.e. about 0.45%), equalling a saving of about €0.32 and €0.38 per year per person of the target group. Every euro invested in the sensitisation campaign would save €3.6 to the health care payer on the long term.

Table 3: Cost (in 2014 €) per stage per six months, separated according to phase

	D&T			Intense FU			Long term FU		
	HC payer	*patient*	*prod. loss*	*HC payer*	*patient*	*prod. loss*	*HC payer*	*patient*	*prod. loss*
BCC <1cm	196	34	0	119	22	0	82	46	0
BCC 1-2cm	211	37	0	128	24	0	89	49	0
BCC>2cm	227	40	0	137	26	0	95	53	0
BCC aggr. hist.	227	40	0	137	26	0	95	53	0
SCC 0-I-II	243	17	0	18	13	13	9	7	0
SCC III	1,396	217	0	91	24	24	45	12	0
SCC IV	1,659	262	0	91	24	24	45	12	0
MSC 0-I	1,891	161	2,663	385	71	1,872	231	41	26
MSC II	2,119	244	1,213	318	60	1,872	258	43	26
MSC III	4,737	200	6,591	1,082	72	11,864	822	72	3,401
MSC IV	51,034	344	6,591	6,758	147	16,688	1,401	141	3,401
Death*	-	-	-	-	-	-	-	-	43,200

D&T: Diagnosis and treatment; hist.: histology; prod.: productivity

** (Cleemput et al., 2012; Hakkaart-van Roijen, 2010)*

Cost-effectiveness of a hypothetical sensitisation campaign and a ban on sunbed use

Impact on skin cancer mortality

Based on the relative risks on skin cancer found in published literature (cf. supra), universal prevention of skin cancer would lead to a reduction in the prevalence of diagnosed SCC and MSC, by affecting the transition from 'free of events' to 'undiagnosed lesion'. Our analysis showed that after 50 years, the sensitising campaign and the ban on sunbed use would lead to a reduction in the prevalence of diagnosed MSC stage I of 11.3% (absolute numbers: 10,954 in males and 15,053 in females) and 8.6%

(absolute numbers: 9,491 in males and 11,335 in females) respectively. The ban on sunbed use was shown to also reduce the prevalence of SCC with 22.7% (absolute numbers: 35,934 in males and 52,565 in females). Due to this decrease in the prevalence of SCC and MSC, less tumours would progress to later stages, because of which a reduction in skin cancer mortality is to be expected. In our model, over a period of 50 years, 3,991 deaths were estimated to be avoided by means of an annual sensitisation campaign (1,593 in males and 2,398 in females) and 3,927 by means of a ban on public sunbed use (1,600 in males and 2,327 in females).

Cost-effectiveness of universal skin cancer prevention

Table 6 shows the results of the cost-effectiveness analysis of both prevention programs. Both programs would lead to a gain in QALYs and cost-savings, making them dominant prevention strategies. When both interventions would be implemented simultaneously, more QALYs could be gained and more costs could be saved than implementing only one of them.

The effect of a shorter or longer induction period was tested and showed that the strategy of a ban on sunbed use remained cost-saving in case of a 10 year- or 30 year-period. A one-way sensitivity analysis of both prevention strategies showed the most influencing parameters to be the utility of skin cancer patients, the discount rate of costs and health effects, the direct cost of diagnosis and treatment of MSC stage III-IV, the relative risk of sunburn in case of a prevention campaign, the relative risk of MSC and SCC if sunbed use and the incidence of MSC, the incidence of MSC and the mortality of MSC stage III and IV (Figure 1). The higher the utility of skin cancer, the direct cost of MSC stage III-IV, the relative risk of MSC or SCC if sunbed use, the effect of the campaign of sunburn and the incidence of MSC, the better the cost-effectiveness. The higher the direct cost of MSC stage III-IV, the relative risk of MSC or SCC if sunbed use, the effect of the campaign of sunburn, the incidence and the mortality rate of MSC, the better the cost-effectiveness. The higher the utility of MSC and SCC and the discount rate, the worse the ICER(Figure 1). These planes show that all simulations are located in the south-east quadrant and hence are cost-saving, showing the robustness of the results.

Table 4: Total current and future societal cost of skin cancer in Belgium, in 2014 euro (calculated with annual inflow)

	MALES		FEMALES		TOTAL (incl. death)			Total cumulative cost 2014-2034	Total cumulative cost 2014-2064
	MSC	**NMSC**	**MSC**	**NMSC**	**MSC**	**NMSC**	**TOTAL**		
Health care payer	€ 17,574,784	€ 12,791,731	€ 20,289,465	€ 13,983,486	€ 37,864,249	€ 26,775,217	€ 64,639,466	€ 1,909,776,064	€ 5,243,814,688
Patient	€ 893,220	€ 5,102,829	€ 1,293,760	€ 5,683,730	€ 2,186,979	€ 10,786,559	€ 12,973,539	€ 341,834,700	€ 993,608,874
Productivity loss	€ 12,769,907	€ 9,191	€ 16,496,350	€ 16,841	€ 29,266,257	€ 26,032	€ 29,292,288	€ 931,099,033	€ 1,878,309,125
Total	**€ 31,237,910**	**€ 17,903,750**	**€ 38,079,575**	**€ 19,684,057**	**€ 69,317,485**	**€ 37,587,808**	**€ 106,905,293**	**€ 3,182,709,797**	**€ 8,115,732,687**

Table 5: Results from the economic impact analysis, showing cumulative costs over 50 years (calculated with inflow)

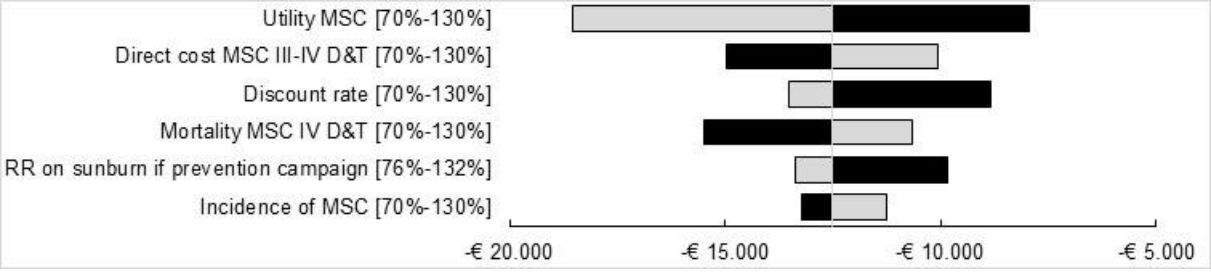
	Cost of intervention	Cost for health care payer	Cost for patient	Cost productivity loss	Total cost	Total extra cost from societal perspective	Total extra cost from health care payer perspective*
No prevention strategy	€ 0	€ 5,243,814,688	€ 993,608,874	€ 1,878,309,125	€ 8,115,732,687		
Sensitisation campaign	€ 39,219,386	€ 5,062,395,121	€ 987,492,778	€ 1,798,897,062	€ 7,888,004,347	-€ 227,728,340	-€ 142,200,181
Ban on sunbed use	€ 0	€ 5,076,473,226	€ 981,978,239	€ 1,819,282,111	€ 7,877,733,575	-€ 237,999,112	-€ 167,341,463

**Health care payer perspective = government, excl. patient co-payment*

Table 6: Results from the cost-effectiveness analysis of universal prevention of skin cancer, expressed per 1,000 persons (calculated without inflow)

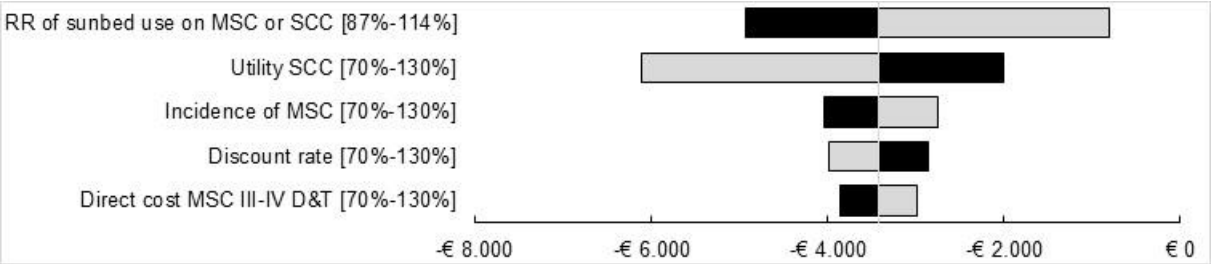
	QALYs		Costs		Incremental QALYs		Incremental costs		ICER	
	males	*females*	*males*	*females*	*males*	*females*	*males*	*females*	*males*	*females*
No prevention strategy	18,876	20,856	€ 669,861	€ 977,368						
Sensitisation campaign	18,877	20,857	€ 654,587	€ 959,957	1.39	1.39	-€ 15,273	-€ 17,411	cost-saving	
Ban on sunbed use	18,881	20,862	€ 649,975	€ 956,984	4.81	5.94	-€ 19,886	-€ 20,384		
Both interventions simultaneously	18,882	20,863	€ 641,858	€ 942,074	5.65	7.21	-€ 28,002	-€ 35,294		

Figure 1a: One-way sensitivity analysis: tornado-diagram showing the most influencing parameters on the cost-effectiveness of a sensitizing prevention campaign in females



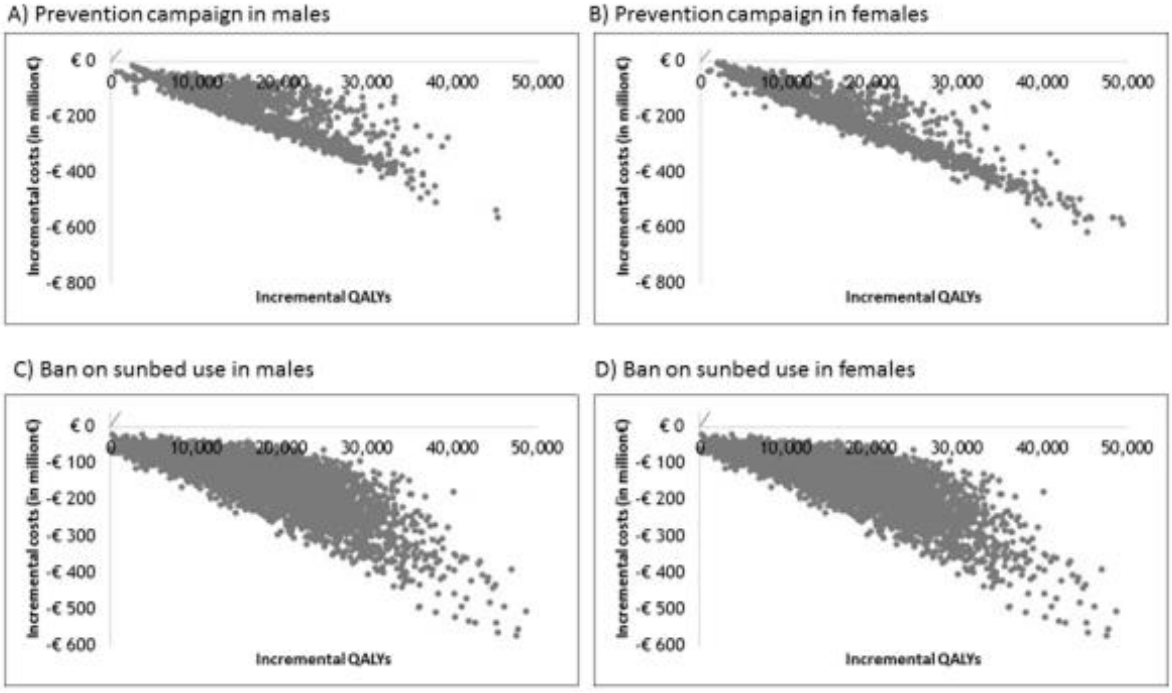
Dark-coloured bars = maximum parameter value; light-coloured bars = minimum parameter value
Range of variation in relative terms between brackets
D&T: diagnosis & treatment; RR: relative risk

Figure 1b: One-way sensitivity analysis: tornado-diagram showing the most influencing parameters on the cost-effectiveness of a total ban on sunbed use in females



Dark-coloured bars = maximum parameter value; light-coloured bars = minimum parameter value
Range of variation in relative terms between brackets
D&T: diagnosis & treatment; RR: relative risk

Figure 2: Cost-effectiveness planes displaying the results of the 5,000 simulations



DISCUSSION

In order to perform the bottom-up cost analysis, individual skin cancer patient cost data were aggregated to the national level based on skin cancer epidemiologic data. Although a bottom-up approach is more time-consuming, it has the advantage of providing more detailed information on the incurred costs. Moreover, it has been shown that the self-reported health care use of responders to surveys does not differ significantly from the observed health care use in the total population and that such a survey is a valid instrument to estimate health care use, especially for general practitioner consultations and inpatient care (Agerholm, Bruce, Ponce De Leon, & Burström, 2015; Van der Heyden, De Bacquer, Tafforeau, Charafeddine, & Van Herck, 2016). Specialist consultations tend to be underestimated when self-reported, which makes the current cost-analysis rather conservative. The analysis on the burden of skin cancer showed that if the rising incidence trend continues, the skin cancer health burden in Belgium will triple within the next 20 years. In comparison, a recent study in the United States estimated MSC incidence rates to double from 2011 to 2030 (Guy et al., 2015). Tromme et al. have previously assessed the cost of MSC treatment by means of 145 hospital bills and 253 patient questionnaires from one hospital (Cliniques Universitaires St-Luc) (Tromme, 2015). The cost they calculated for treatment of MSC stage IV was lower than our result. Most probably, this has to do with the high cost of new treatment drugs for the management of melanoma stage IV, which were not yet used in the time Tromme et al. did their research. Besides, they didn't include costs due to productivity loss. The current annual total cost for skin cancer in Belgium was estimated to be €107 million in this study (for a population of 8.8 million Belgian adults), of which almost €65 million is to be paid by the health care payer (government), resulting in about 0.18% of the total public health care budget in Belgium. The result is comparable to other European studies. A Danish study (5.5 million inhabitants) found that in 2010 direct skin cancer cost accounted for €33.3 million or 0.2% of the Danish health care budget (Bentzen et al., 2013). In Sweden (9 million inhabitants in 2005) the total societal cost for MSC was €79.7 million and €36.2 million for NMSC in 2005 (Tinghog, Carlsson, Synnerstad, & Rosdahl, 2008). A bottom-up cost-of illness study in England calculated an annual direct cost of 106.4 million pound in 2008 (€124.7 million in 2015) for MSC and NMSC (Vallejo-Torres, Morris, Kinge, Poirier, & Verne, 2014). A top-down method generated a similar result. This is relatively low compared to the Belgian situation (direct cost estimated to be about €78 million) since there are almost 5 times more inhabitants in England. However, all these studies were performed some years ago, not yet taking into account the recent, more expensive therapies to treat metastatic MSC, which can bias the comparison with our study results. According to our results, MSC was responsible for 65% of the medical costs, in contrast to a study examining the hospitalisation costs of skin cancer in Germany (Stang et al., 2008). The latter study concluded that NMSC-related costs for hospitalisations were about twice the rates of MSC. Nonetheless, in Sweden and Denmark the proportion of cost due to MSC was similar to the Belgian proportion (resp. 68.7% and 59%, although the latter only included direct costs) (Bentzen et al., 2013; Tinghog et al., 2008). Additionally, the cost calculations were probably affected by the registration method. Only the first NMSC lesion was registered in the Dutch database. Although we tried to account for the risk of a recurrent and a subsequent lesion, the total NMSC-related cost tends to be underestimated in our study, which could have influenced the balance between MSC and NMSC-related costs. In comparison, the annual societal

cost of established arteriosclerotic cardiovascular disease in Belgium was €2,1 billion in 2004 (Vlayen et al., 2008), and all brain disorders combined accounted for €10.6 billion in 2004 (Schoenen, Gianni, Schretlen, & Sobocki, 2006), suggesting that the economic burden of skin cancer is relatively low. However, it is expected that the estimated total economic burden of skin cancer is an underestimation of the real cost of skin cancer, as only the first NMSC was registered in the epidemiologic data from the Dutch cancer registry (IKNL). Projections to 2034 showed an estimated annual discounted cost of €142 million, and a total cumulative cost of €3 billion. This estimated future annual cost of 2034 is in line with other studies that made projections into the future. In England, a projection from 2008 to 2020 showed almost a doubling in the annual cost of skin cancer (106.4 million pound to 190.5 million pound) (Vallejo-Torres et al., 2014).

The results at hand showed that an on average €155 million of the health care budget could be redirected to other diseases by implementing a skin cancer prevention campaign or a ban on sunbeds in Belgium. Although a total ban on sunbed use would gain more health benefits, both interventions are cost-saving on the long term and thus dominant. However, the extra costs for the individuals as a consequence of the prevention campaign, such as extra sunscreen and sun-protecting clothing was not included in our model, since there is no accurate information on these costs in the control group (i.e. without intervention). Nonetheless, suppose an extra cost of €5 per adult would be assumed, then the sensitisation campaign would not be cost-effective anymore. The sensitivity analysis revealed that the higher the medical costs of treating metastatic MSC, the more cost-effective prevention would be, since the financial benefit of prevention would be higher. Recently, new expensive treatments for metastatic MSC were introduced and it is expected that in the future treatment costs will continue to rise, which further favours prevention interventions for MSC. However, a major challenge is to create the desired altered behaviour by implementing a prevention campaign. Consequently, a total ban on sunbed use could be a relatively more easy way to achieve a specific behaviour.

To our knowledge, no similar cost-effectiveness analysis in combination with an economic burden-of-illness and budget impact analysis of universal prevention of skin cancer has been performed up to now. Gordon & Rowell (2015) included seven studies in their review of the cost-effectiveness of - what they call- primary prevention. Although all studies had different designs and context, they concluded that skin cancer primary prevention programs or policies are consistently cost-effective and may even be cost-saving for governments in the near future. In Australia, the SunSmart program has been evaluated twice, by Carter et al. (1999) and later on by Shih et al. (2009). We adopted the method of Carter et al., namely the evaluation of the effectiveness of the program on skin cancer incidence in an indirect way, by the effect on the prevalence of sunburns. Carter et al. included an induction period of 5 years for MSC and 15 years for NMSC before the reduced incidence is realised. Their analysis resulted in the prevention of 4,300 deaths over 20 years, and net savings to government of AUD 103 million. The study of Shih et al. obtained similar results with a return of investment of AUD 3.6 per invested dollar. The major differences between the study of Shih et al. and our study are their measurement of the program effectiveness, namely directly on the skin cancer incidence, their final outcome in the economic analysis which were DALYs, the comparator of their analysis being a less intense program with less invested money and their perspective which was only from the health care payer. Additionally, the recent study

of Doran et al. evaluated the cost-effectiveness of the implementation of three skin cancer mass media campaigns in New South Wales (Australia) and found a return on investment of AUD 3.85 per invested dollar (Doran et al., 2016).

Some limitations of our analysis should be acknowledged. First, since for some skin cancer stages the sample of returned patient questionnaires was too small, we had to rely on expert opinion and literature data to calculate the medical costs for these groups. The indirect costs were derived from the small sample data and could therefore be partly biased. However, the prevention strategies remained cost-saving even without inclusion of productivity loss. Second, the simulation of the prevention programs is hypothetical; a trial-based analysis may be beneficial. Therefore, the effect of a prevention campaign was deduced from the Australian SunSmart program. However, it is not known if such a campaign would have a similar relative effect on sunburn in Belgium. A German study evaluating the effectiveness of skin cancer information campaigns during the last 16 years found a relative risk of 0.68 to get sunburned in presence of a campaign, which denotes a lower effectiveness of the campaign than the SunSmart campaign (Breitbart, Greinert, & Volkmer, 2006). However, the sensitivity analysis acknowledged this uncertainty and showed that the intervention would still be cost-saving in case of a lower effectiveness. Third, in Belgium there is no accurate registration of NMSC. Therefore, we relied on epidemiologic figures of the Dutch cancer registry, and applied a correction factor to it based on the incidence- as well as mortality rate of MSC in both countries (International Agency for Research on Cancer, 2012b). As already stated, it should be noted that only the first NMSC lesion was registered. Although we tried to account for subsequent and recurrent lesions in the model, it is expected that the real incidence, prevalence and costs of NMSC is larger than simulated by our model. Fourth, accurate information on the natural progression of skin cancer is not available. Therefore, in our model, the natural progression was estimated based on calibration. This is generally a more reliable approach than making assumptions on parameters based on limited studies. Lastly, it should be noted that the findings of this study cannot be directly transferred to other countries as some key parameters are context-specific such as the incidence of MSC and the medical costs for treatment and follow-up of advanced tumours. It is expected that in countries with a higher incidence of MSC, these evaluated prevention strategies would lead to higher cost-savings.

CONCLUSIONS

This analysis estimated the prevalence of skin cancer to triple in the next 20 years. A hypothetical sensitising campaign and a ban on sunbed use were shown to be two universal prevention strategies which can offer excellent value for money and even save money not only for the health care payer but also for society as a whole. These results can aid policy makers and clinicians to promote UV protection strategies on a long-term basis.

APPENDIX

Appendix Table 1: Prevalence of undiagnosed lesions

Parameter	Input value						
	18-29y	***30-39y***	***40-49y***	***50-59y***	***60-69y***	***70-79y***	***79+y***
BCC <1cm M	0.015%	0.135%	0.377%	0.699%	1.528%	3.022%	3.809%
BCC <1cm F	0.035%	0.150%	0.633%	0.799%	1.419%	2.033%	2.275%
BCC 1-2cm M	0.008%	0.075%	0.209%	0.387%	0.846%	1.674%	2.109%
BCC 1-2cm F	0.019%	0.083%	0.350%	0.443%	0.786%	1.126%	1.260%
BCC >2cm M	0.002%	0.021%	0.059%	0.109%	0.238%	0.470%	0.592%
BCC >2cm F	0.005%	0.023%	0.098%	0.124%	0.221%	0.316%	0.354%
BCC aggr. hist. M	0.011%	0.101%	0.282%	0.522%	1.141%	2.257%	2.844%
BCC aggr. hist. F	0.026%	0.112%	0.472%	0.597%	1.059%	1.518%	1.699%
SCC stage 0-II M	0.000%	0.001%	0.002%	0.013%	0.048%	0.268%	0.967%
SCC stage 0-II F	0.001%	0.002%	0.010%	0.033%	0.095%	0.222%	0.419%
SCC stage III M	0.000%	0.000%	0.000%	0.001%	0.006%	0.031%	0.112%
SCC stage III F	0.000%	0.000%	0.001%	0.004%	0.011%	0.026%	0.049%
SCC stage IV M	0.000%	0.000%	0.000%	0.000%	0.001%	0.007%	0.026%
SCC stage IV F	0.000%	0.000%	0.000%	0.001%	0.003%	0.006%	0.011%
MSC stage I M	0.065%	0.173%	0.328%	0.527%	0.805%	1.156%	1.132%
MSC stage I F	0.128%	0.311%	0.488%	0.543%	0.704%	0.767%	0.502%
MSC stage II M	0.019%	0.049%	0.094%	0.151%	0.230%	0.331%	0.324%
MSC stage II F	0.029%	0.070%	0.109%	0.122%	0.158%	0.172%	0.112%
MSC stage III M	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%
MSC stage III F	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%
MSC stage IV M	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%
MSC stage IV F	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%

M: Males F: Females

Source: (Hoorens et al., 2016)

Appendix Table 2: Incidence and natural progression of skin cancer lesions

Parameter	Input value						
	18-29y	***30-39y***	***40-49y***	***50-59y***	***60-69y***	***70-79y***	***79+y***
INCIDENCE							
BCC M[a]	0.001%	0.004%	0.013%	0.024%	0.053%	0.101%	0.107%
BCC F[a]	0.002%	0.006%	0.024%	0.029%	0.055%	0.075%	0.078%
SCC M[a]	0.000%	0.000%	0.001%	0.005%	0.018%	0.053%	0.123%
SCC F[a]	0.000%	0.000%	0.002%	0.006%	0.017%	0.038%	0.076%
MSC I M[b]	0.002%	0.004%	0.007%	0.010%	0.013%	0.019%	0.017%
MSC I F[b]	0.005%	0.011%	0.017%	0.016%	0.015%	0.017%	0.009%
NATURAL PROGRESSION							
BCC[c]	12.5%						
SCC stage 0-II => III[d]	1.0%						
SCC stage III => IV[e]	7.0%						
MSC I => II/III[e]	0.4%						
MSC II => III[e]	1.7%						
MSC II => IV[e]	1.5%						

a *(Integraal Kankercentrum Nederland, 2011); b (Belgian Cancer Registry, 2013); c (Kirkup & De Berker, 1999); d (Smoller, 2006); e calibration*

Appendix Table 3: Risk of metastases, of developing MSC after NMSC and mortality rates

Parameter	Input value						
	18-29y	***30-39y***	***40-49y***	***50-59y***	***60-69y***	***70-79y***	***79+y***
PROGRESSION TO METASTASES, AFTER TREATMENT							
SCC[a]				0.23%			
MSC stage I => MSC stage III[b]				0.07%			
MSC stage I => MSC stage IV[b]				0.07%			
MSC stage II => MSC stage III[b]				0.47%			
MSC stage II => MSC stage IV[b]				0.47%			
MSC stage III => MSC stage IV[b]				2.26%			
RELATIVE RISK OF DEVELOPING MSC AFTER DIAGNOSES OF NMSC							
MSC after BCC[c]				3.28			
MSC after SCC[c]				3.62			
MORTALITY RATES							
Mortality due to skin cancer (first year)							
MSC stage IV[d]				26.66%			
SCC stage IV[e]				23.70%			
Mortality due to skin cancer (follow-up)							
MSC stage IV[d]				M: 12.45% F: 7.65%			
SCC stage IV[f]				M: 6.33% F: 9.71%			
Mortality due to other causes[g]							
Male	0.04%	0.05%	0.12%	0.33%	0.76%	1.97%	3.85%
Female	0.01%	0.02%	0.04%	0.13%	0.30%	0.71%	2.46%

M: male; F: female

a (Rowe et al., 1992); b (Leiter et al., 2012); c (Rees et al., 2014); d (Belgian Cancer Registry, 2014) corrected for new therapies; e (Council of the European Union, 2010); f (Hollestein et al., 2012); g Belgian life tables 2012

Health-related quality of life: utilities

Undiagnosed BCC, SCC stage 0-II and MSC stage I were assigned the same utility as the population norm, which is 0.81 (Scientific Institute of Public Health., 2013). The utility for undiagnosed SCC stage III-IV and MSC stage III-IV was calculated as the average of the population norm and the utility for diagnosis and treatment. The sample size of completed patient questionnaires for SCC and MSC stage II-III and IV was too small to have sufficient sample power, so the utilities of these stages (diagnosed) were calculated based on the ratio of the utilities in these stages compared to stage I, as described by Tromme et al. (2014). The utility for BCC patients, who are in treatment or intense follow-up is derived from the study of Gaulin et al. (2015). The utility for patients in long term follow-up for BCC, SCC 0-II and MSC 0-I and II was defined to be the same as the population norm, since it is assumed that once the lesion has been excised, the quality-of-life will return to baseline on the long term.

Appendix Table 4: utilities assigned to the model states

Parameter	Input value						
	18-29y	***30-39y***	***40-49y***	***50-59y***	***60-69y***	***70-79***	***79+***
General population[a]	0.891	0.844	0.833	0.791	0.789	0.768	0.652
BCC undiagnosed[ad]	0.891	0.844	0.833	0.791	0.789	0.768	0.652
D&T BCC[b]	0.869	0.822	0.811	0.769	0.767	0.746	0.630
intensive FU BCC[b]	0.869	0.822	0.811	0.769	0.767	0.746	0.630
Long term FU BCC[ad]	0.891	0.844	0.833	0.791	0.789	0.768	0.652
SCC 0-II undiagnosed[ad]	0.891	0.844	0.833	0.791	0.789	0.768	0.652
SCC III undiagnosed	0.710	0.663	0.652	0.610	0.608	0.587	0.471
SCC IV undiagnosed	0.730	0.683	0.672	0.630	0.628	0.607	0.491
SCC 0-II D&T[c]	0.611	0.564	0.553	0.511	0.509	0.488	0.372
SCC III D&T	0.529	0.482	0.471	0.429	0.427	0.406	0.290
SCC IV D&T	0.569	0.522	0.511	0.469	0.467	0.446	0.330
SCC 0-II intense FU[c]	0.786	0.739	0.728	0.686	0.684	0.663	0.547
SCC III intense FU	0.699	0.652	0.641	0.599	0.597	0.576	0.460
SCC IV intense FU	0.781	0.734	0.723	0.681	0.679	0.658	0.542
SCC 0-II long term FU[ad]	0.891	0.844	0.833	0.791	0.789	0.768	0.652
SCC III long term FU	0.785	0.738	0.727	0.685	0.683	0.662	0.546
SCC IV long term FU	0.878	0.831	0.820	0.778	0.776	0.755	0.639
MSC I undiagnosed[ad]	0.891	0.844	0.833	0.791	0.789	0.768	0.652
MSC II undiagnosed[ad]	0.891	0.844	0.833	0.791	0.789	0.768	0.652
MSC III undiagnosed	0.751	0.704	0.693	0.651	0.649	0.628	0.512
MSC IV undiagnosed	0.774	0.727	0.716	0.674	0.672	0.651	0.535
MSC I D&T[c]	0.761	0.714	0.703	0.661	0.659	0.638	0.522
MSC II D&T	0.654	0.607	0.596	0.554	0.552	0.531	0.415
MSC III D&T	0.610	0.563	0.552	0.510	0.508	0.487	0.371
MSC IV D&T	0.658	0.611	0.600	0.558	0.556	0.535	0.419
MSC I intense FU[c]	0.780	0.733	0.722	0.680	0.678	0.657	0.541
MSC II intense FU	0.774	0.727	0.716	0.674	0.672	0.651	0.535
MSC III intense FU	0.688	0.641	0.630	0.588	0.586	0.565	0.449
MSC IV intense FU	0.769	0.722	0.711	0.669	0.667	0.646	0.530
MSC I long term FU[ad]	0.891	0.844	0.833	0.791	0.789	0.768	0.652
MSC II long term FU[ad]	0.891	0.844	0.833	0.791	0.789	0.768	0.652
MSC III long term FU	0.785	0.738	0.727	0.685	0.683	0.662	0.546
MSC IV long term FU	0.878	0.831	0.820	0.778	0.776	0.755	0.639
False positive result on screening[d]	0.884	0.837	0.826	0.784	0.782	0.761	0.645

a (Scientific Institute of Public Health., 2013)

b (Gaulin, Sebaratnam, & Fernandez-Penas, 2015)

c patient questionnaires

d assumption

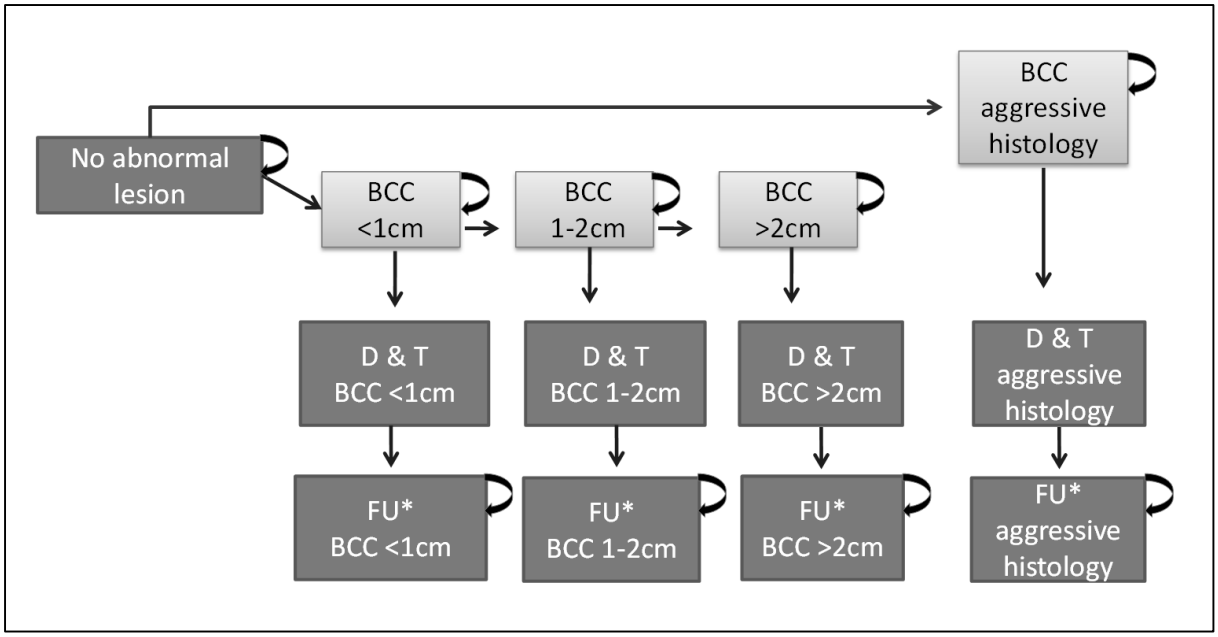
Natural evolution of skin cancer

Information on the natural evolution of undiagnosed melanoma tumours is lacking. Therefore, model calibration was applied by manually searching for the best combination of parameter values, as to match the modelled outputs to the observed evidence on the outputs, in this case the number of melanoma deaths. In Belgium, every year about 450 people die from skin cancer. Over 20 year this would mean about 9,000 deaths (without taking the rising trend in incidence into account). Since SCC lesions are under registered in Belgium, the actual number of deaths is estimated to be higher. The output of the model, in terms of number of skin cancer deaths after 20 year, was matched to this expected 9,000 deaths based on estimation of the natural progression. When this natural progression from MSC stage I was set at 0.4% and from MSC stage II at 1.7% (to stage III) 1.5% (to stage IV), the output of the model showed 11,100 deaths over 20 years, which is in line with the estimated number of deaths in reality. Natural progression of BCC was derived from the study of Kirkup et al. (1999), showing an evolution of 1 cm per 3.8 years or 1.2 mm per 6 months. The transition risk from SCC stage 0-II to stage III or IV was estimated as 0.5% per 6 months (Smoller, 2006).

Appendix Figure 1: Visualisation of the Markov model

BCC: Basal cell carcinoma; SCC: Squamous cell carcinoma; FU: Follow-up; D & T: Diagnosis and treatment. Light-coloured states correspond to undiagnosed cancer

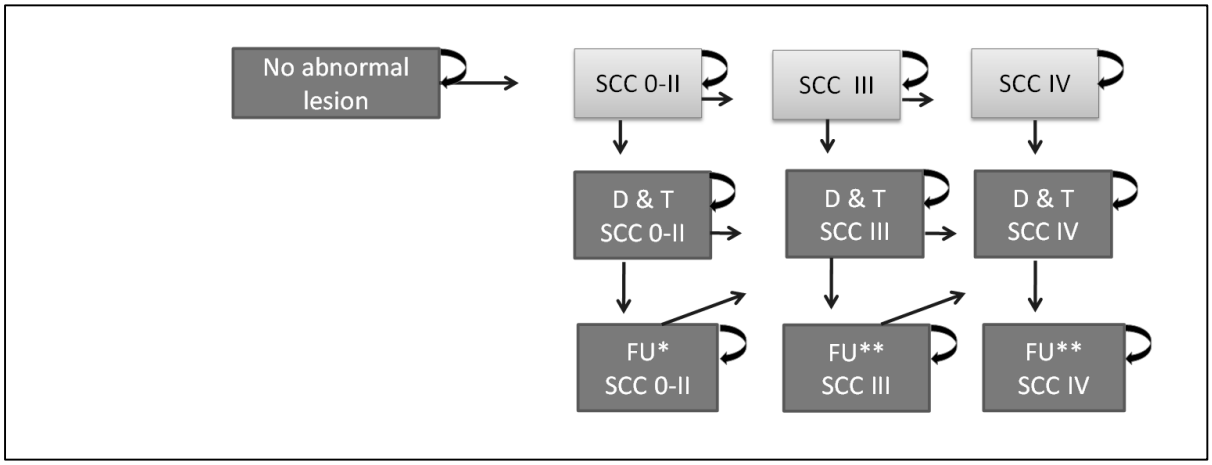
a) Markov model for BCC lesions



**FU is divided in intense FU (3 cycles) and long term FU*

From BCC one can also develop a melanoma lesion

b) Markov model for SCC lesions

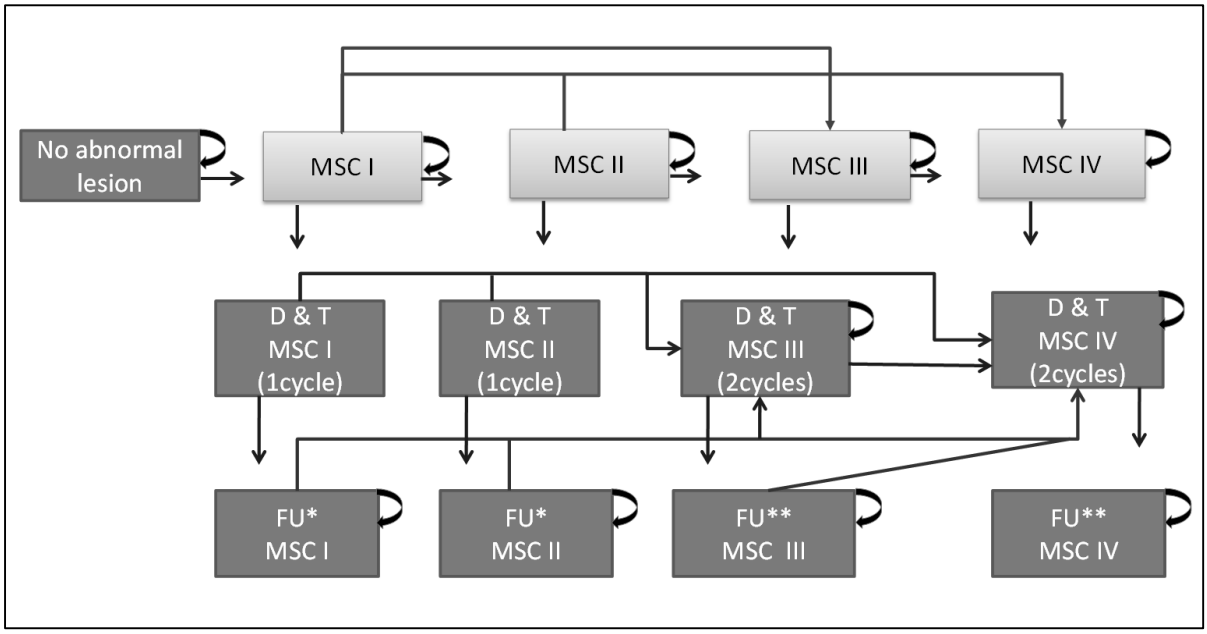


**FU is divided in intense FU (3 cycles) and long term FU*

*** FU is divided in intense FU (8 cycles) and long term FU*

From SCC one can also develop a melanoma lesion

c) Markov model for MSC lesions



**FU is divided in intense FU (3 cycles) and long term FU*

*** FU is divided in intense FU (8 cycles) and long term FU*

Part 2: Original research studies: health economic evaluations in the continuum of prevention

2.2. Selective prevention interventions

2.2.1. Cost-effectiveness and budget impact analysis of the population-based screening program for breast cancer

Maaike Fobelets*, Lore Pil*, Koen Putman, Jeroen Trybou & Lieven Annemans. Cost-effectiveness and budget impact analysis of the population-based screening program for breast cancer. *Journal of Medical Screening.* (*Paper submitted).*

** Shared first authorship*

ABSTRACT

Introduction Belgium has the highest incidence of breast cancer (BC) in Europe. A biennial mammography population-based screening program for women aged 50 to 69 years has been organised in Flanders (Belgium) since 2001. An economic analysis was performed to evaluate the cost-effectiveness of the current BC screening program in order to assess whether continuation of the current screening program is efficient.

Methods A screening decision tree and a state-transitional Markov model were developed to calculate the costs and health effects over a period of 20 years. Medical and non-medical costs, quality-adjusted life-years and mortality were estimated in order to determine the incremental cost-effectiveness ratio of the screening program, compared to no screening program. A budget impact analysis estimated the impact of the screening program on the healthcare budget.

Results Assuming a threshold value of €35,000/QALY gained, the BC screening program in Flanders was predicted to be cost-effective with an ICER of €28,428/QALY and a mortality reduction of 14.0% over a period of 20 years. The parameters with the highest influence on the ICER were the utility of BC stage I treatment and follow-up, absenteeism due to a mammography and the natural progression of BC. The budget impact analysis indicated that, beside the organisational cost, the screening program induces extra costs for both patient and health care payer.

Conclusion The current population-based BC screening program is cost-effective in Flanders and appears to be effective in reducing BC mortality, despite the possible adverse effects and the induced treatment costs related to the biennial mammography screening program

INTRODUCTION

No other European country recorded a higher incidence of breast cancer (BC) than Belgium, namely 147.5 cases per 100,000 women (International Agency for Research on Cancer, 2012a). The BC screening program in Flanders was introduced in 2001 after a long history of opportunistic screening. Today, women of 50 to 69 years are invited biennially for a screening mammography, in accordance with the European guidelines for BC screening and diagnosis (Perry et al., 2008). Over the last decade, several cost-effectiveness studies on BC screening have been published, all focussing on certain aspects of breast cancer screening. Some evaluated the BC screening program as currently implemented in the particular country (Arrospide et al., 2016; Carles et al., 2011; Pharoah, Sewell, Fitzsimmons, Bennett, & Pashayan, 2013), others evaluated different screening intervals (Gocgun et al., 2015; Mittmann et al., 2015; Rojnik, Naversnik, Mateovic-Rojnik, & Primiczakelj, 2008), different screening techniques (Melnikow et al., 2013; Wang, Merlin, Kreisz, Craft, & Hiller, 2009) or different age limits (Rafia et al., 2016; Rashidian, Barfar, Hosseini, Nosratnejad, & Barooti, 2013). However, few of these studies have looked at the budget impact of BC screening. Moreover, possible drivers of the results, such as the impact of the uncertainty associated with anxiety due to a false-positive result as well as productivity losses have rarely been included. In addition, results of these published cost-effectiveness studies from other jurisdictions cannot be directly transferred to the situation in Flanders, as country- or region-specific demographic, epidemiologic as well as screening-related parameters should be taken into account. Since a health economic analysis of the current population-based BC screening program in Flanders has never been performed in the past, the aim of this study was to assess the overall cost-effectiveness and budget impact of the program, taking into account the uncertainty in the above mentioned parameters and with the aim to explore all possible drivers of the result.

METHODS

Screening strategy

The organised BC screening program consists of a biennial mammography screening for women of 50 to 69 years, of which 50.2% participated in 2013. Women with a history of BC (less than ten years ago) and women who underwent an opportunistic mammography less than two years ago are not invited to the screening program. All screening mammograms undergo double reading by two independent radiologists. In case of discordant double reading results, arbitration by a third radiologist is used to find a consensus. After a positive test result extra diagnostic tests such as a breast ultrasound are performed; after a negative test result, the woman will be re-invited after two years. An estimated 15% of the target group participates in spontaneous opportunistic screening instead of participating in the organised the screening program.

Model design

A Markov model with a 20-year time horizon and a one-year cycle length was developed consisting of several disease states categorised according to the Tumour-Node-Metastasis-staging (Sobin et al., 2009). The following states were included in the Markov model: unidentified ductal carcinoma in situ

(DCIS); unidentified BC stage I, II, III or IV; identified BC stage I, II, III or IV in treatment; intense follow-up (year 1 to 4) of these stages; and long-term follow-up (year 4+) (Appendix Figure 1). The comparator of the screening program was the natural history of BC in the presence of the above mentioned 15% spontaneous opportunistic screening. At the start of the model, persons in the target population were free of lesions or had an unidentified lesion. BC could be detected through the population-based screening program, spontaneous opportunistic mammography or clinically, based on symptoms. Annually, cancer-free people could develop a tumour, people with an unidentified tumour could be detected, diagnosed and receive treatment and in the next years progress to follow-up. The treatment phase lasted one year after which women progressed to the follow-up phase (separated into intense FU and long term FU). During treatment and follow-up, women could still progress to regional metastasis (stage III) or to distant metastasis (stage IV). Mortality was incorporated as BC-related mortality, only applied to women with BC stage III or IV, and as mortality from other causes. The cost-effectiveness of the screening program was evaluated by calculating the incremental cost-effectiveness ratio (ICER), defined as the ratio of difference in costs to the difference in effectiveness between intervention and comparator. The budget impact analysis estimated the net cumulative cost of the screening program (and consequent examinations, treatment and follow-up) for the healthcare payer (i.e. government) over a period of 20 years, while accounting for an annual inflow of new 50 year olds.

Epidemiological and clinical inputs

Epidemiologic data were based on a combination of the best available data from the Belgian Cancer Registry, life tables and data from published literature (Appendix Table 1-4). Annual progression probabilities were calculated by converting sojourn times[12], based on tumour size, into annual progression probabilities assuming a basic Poisson process (Harris & Hellman, 1996; Tan et al., 2013). Risk of metastases was retrieved from the study of Siponen et al (2013). Disease-specific mortality was obtained from the Belgian Cancer Registry (2014) and mortality from other causes was extracted from the Flemish life tables. Model parameters related to the screening program were obtained from the Flemish Government (Table 1) (Centrum voor Kankeropsporing, 2013).

Health-Economic inputs

All cost calculations were performed from a societal perspective (medical unit costs and days absenteeism are presented in Appendix Table 5-6). Direct medical costs for screening, diagnosis and treatment were based on Belgian data (Broe. Indirect costs of productivity loss were calculated based on the friction cost method (Hakkaart-van Roijen, 2010). The number of days off work due to BC were multiplied with the average cost per working day (Cleemput et al., 2012), weighted for the employment rate, proportion of full-time equivalents and applied to women younger than 65 years. Costs were indexed to year 2014 by using the Health Index (Federale Overheidsdienst Economie KM, 2015). Health effects were calculated as quality-adjusted life years (QALYs), by using (EQ-5D index) utilities, expressing the quality of life with a range from 0 (death) to 1 (perfect health). The utilities for the different

[12] The sojourn time is the time between the onset of the disease (preclinical phase) and the manifestation of clinical symptoms (clinical phase)

health states were age- and gender specific, derived from Flemish as well as international published data (Appendix table 7). A utility loss reflecting the psychological stress due to a false-positive screening result was considered in the model, although there is still debate on the magnitude of this impact (Cockburn, Staples, Hurley, & De, 1994; Johnston, Brown, Gerard, O'Hanlon, & Morton, 1998). According to Johnston et al. (1998), the utility related to a false-positive result is similar to the utility of a true positive result. In our model, the utility of an identified DCIS of BC stage I is about 10% less than the utility of the general population. Therefore a 10% disutility related to a false-positive result was assumed, for a duration of one month. Following the Belgian guidelines, health effects were discounted at 1.5% and costs at 3% (Cleemput et al., 2012).

Table 1: Screening-related parameters from the Flemish screening program

Model parameter	Input value	
	50-59y	*60-69y*
Participation rate screening	49.40%	51.5%
Participation rate extra examinations (after pos. screening result)	91.70%	91.70%
Proportion of screening population with diagnostic mammography*	15.00%	15.00%
Sensitivity screening program for DCIS	83.00%	83.00%
Sensitivity screening program for invasive BC	69.10%	69.10%
Specificity screening program	98.30%	98.30%

BC: Breast cancer DCIS: Ductal carcinoma in situ

Source: Annual report Flemish cancer screening, 2013 (Centrum voor Kankeropsporing, 2013)

** expert opinion*

Sensitivity and scenario analysis

A one-way and probabilistic sensitivity analysis was conducted to identify the uncertainty of parameters and the robustness of the results. The following parameters were included in the one-way sensitivity analysis: costs of the screening program, direct medical costs, days off work due to BC, time off work due to the mammography, incidence of undiagnosed BC stage I, BC mortality rates, test characteristics (screening- and diagnostic mammography), screening participation rate per age group, utilities, participation to further examinations, percentage opportunistic screening, risk on symptoms and BC progression rates. Parameters were varied based on standard error estimates of the literature (if not available ±30% ranges were used). Probability distributions were defined for costs (gamma distribution), utilities, test characteristics of the mammography, participation rate per age-category (beta distribution) and days off work (normal distribution). A probabilistic sensitivity analysis was performed by running 5000 2nd order Monte Carlo simulations and a cost-effectiveness acceptability curve (CEAC) was drawn to inform policy makers on the probability of cost-effectiveness given a certain cost-effectiveness threshold (i.e. willingness to pay). Moreover, the following scenarios were tested: a public health care payer perspective (i.e. exclusion of costs related to productivity loss and costs to be paid by the patient),

worst and best case scenario of the utility of a false-positive result, in which the worst case was an equal value to the utility of BC stage I in treatment and the best case was an equal value to the utility of no abnormal lesion, and a time horizon of 50 years instead of 20 years. In the scenario with a time horizon of 50 years, an annual inflow of new 50-year olds was included, as after 20 years the original cohort is not eligible for screening anymore.

Model outcome validation

The modelled mammography screening resulted in an average annual positivity rate of 2.23% and detection rate of 0.51% over a period of 20 years. These results are in line with the positivity rate of 2.10% and detection rate of 0.55% of the current BC screening program (Centrum voor Kankeropsporing, 2013). Besides, the distribution of the cancer prevalence according to the tumour stage over 20 years in the screening arm was compared to the stage distribution of tumours in 2010 (Belgian Cancer Registry, 2010a). This stage distribution was 40%, 36%, 17% and 7% from stage I to IV in the model, and 43%, 37%, 14% and 7% in real-life, which means that overall estimated stage distribution seemed to approximate the observed stage distribution.

RESULTS

Base case (deterministic)

Over 20 years, the screening program yielded 0.007 QALY per woman of 50 years and older, against an incremental cost of €206 (Table 2), resulting in an incremental cost-effectiveness ratio of €28,428/QALY. Assuming a cost-effectiveness threshold of €35,000/QALY gained (i.e. GDP per capita Belgium) this result shows that the Flemish BC screening program is expected to be cost-effective. The benefit of the screening program is shown in Appendix Figure 2; more early-stage tumours were detected in reference to advanced tumours. The incidence of BC stage IV in the presence of the screening program was predicted to decrease by 14.5% during the 20-year period, in comparison to the situation without screening program. Additionally, over 20 years a mortality reduction of 14.2% was expected due to the screening program. The budget impact analysis showed that the screening program generates more costs for the health care payer (i.e. government) compared to no screening program (Table 3). Over a period of 20 years, the screening program resulted in a net cumulative cost of €492,239,887, or €31 per year per woman from the target group (50-69 year-olds).

Sensitivity and scenario analysis

The results of the one-way sensitivity analysis are depicted in Appendix Figure 3. The most influential parameters were the utility of treatment of BC stage I, the utility of follow-up, absenteeism due to having a mammography, the natural progression of BC and the incidence of BC stage I. A higher utility related to the treatment of BC stage I and the follow-up of BC in general, as well as a higher incidence rate of BC stage I would lead to a better ICER. Higher natural progression rates would also favour the ICER. In the base case no productivity loss was applied to undergoing a mammography, assuming the time women lost due to the mammography screening would be compensated. When applying 2 to 4 hours productivity loss, the ICER would deteriorate to a range of €43,284/QALY to €58,141/QALY. Increasing

the participation rate for screening, usually perceived as one of the key indicators, with 30% relatively (i.e. from 51% to 66%), only slightly ameliorated the ICER. Results from the Monte Carlo simulations, which are mainly plotted in the north-east quadrant of the incremental cost-effectiveness plane (Figure 1), confirmed that the BC screening program induced more costs but was more effective compared to no screening. The probabilistic sensitivity analysis resulted in an ICER of €31,377/QALY (95%CI: €21,973 -54,977/QALY) and a mortality reduction of 14.0% (95%CI: 11.1% – 16.6%). The cost-effectiveness acceptability curve showed that biennial mammography screening was cost-effective in 82.9% of all simulations, given a willingness-to-pay threshold of €35,000/QALY gained (Figure 2). In case of assuming a public health care payer perspective the ICER slightly worsened (Table 2). In the worst case scenario concerning the utility related to a false-positive result, the cost-effectiveness result would deteriorate to €86,486/QALY, in the best case scenario, the ICER ameliorated to €27,042/QALY. Extending the time horizon to 50 years (incl. annual inflow) resulted in a better ICER, namely €13,060/QALY.

Table 2: Results of the cost-effectiveness analysis, with several scenarios

Scenario	Δ Cost (€)	Δ QALY	ICER (€/QALY)	Mortality reduction
Base case deterministic	€ 206	0.007	€ 28,428	14.20%
Public health care payer perspective	€ 215	0.007	€ 29,828	14.20%
Time horizon 50 years *(incl. new inflow)*	€ 219	0.017	€ 13,060	17.80%
Utility false positive: best case	€ 206	0.008	€ 27,042	14.20%
Utility false positive: worst case	€ 206	0.002	€ 86,468	14.20%
Base case probabilistic	€ 195	0.008	€ 31,377	14.10%
(95%CI)	(€149-€305)	(0.002-0.010)	(€21,973-€54,977)	(11.1%-16.6%)

Δ cost: total cost with screening program minus total cost without screening program

Δ QALY: total Quality Adjusted Life Years (QALY) with screening program minus total QALY without screening program

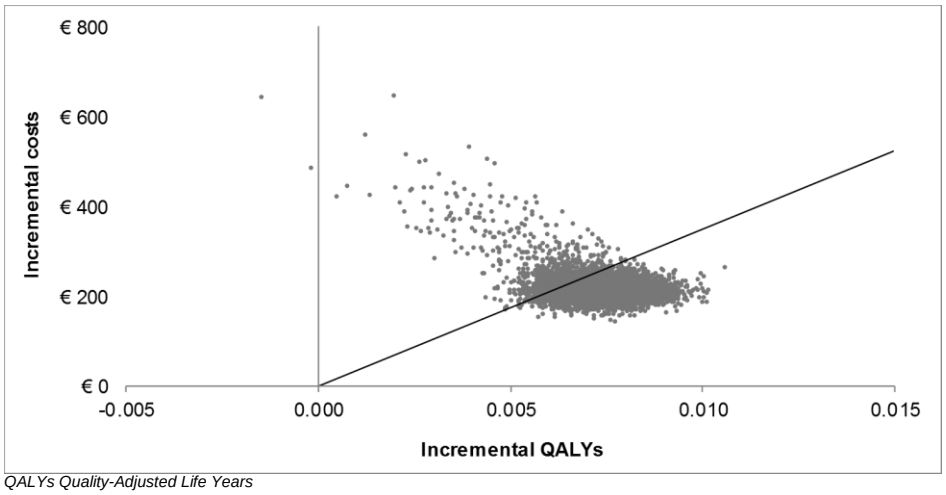
ICER: Incremental cost-effectiveness ratio

Mortality reduction: mortality due to BC without screening program (i.e. non-invited) minus with screening program (i.e. invited)

Table 3: Results of the budget impact analysis (over 20 years)

	Cost health care payer	Costs for organisation of screening	Total extra cost
With screening program	€ 1,424,621,725	€ 53,830,610	€ 492,239,887
Without screening program	€ 986,212,448	€ 0	

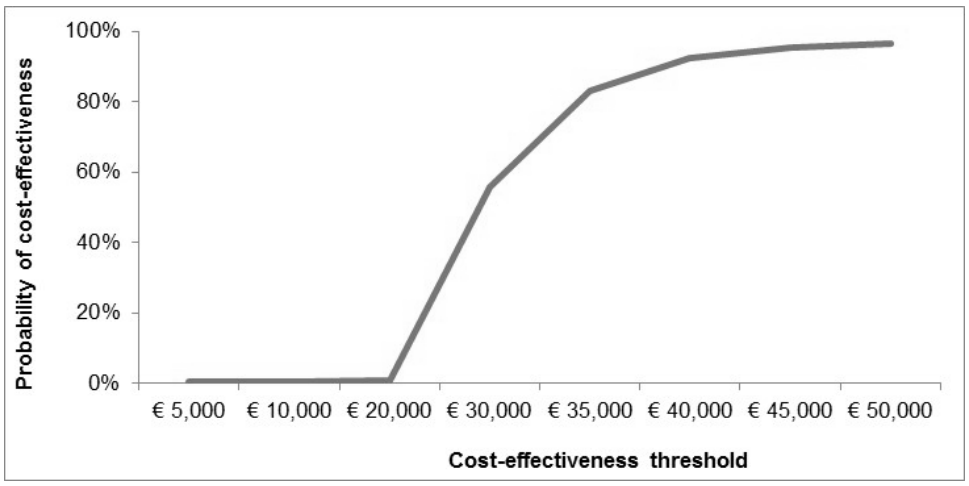
Figure 1: Cost-effectiveness plane



QALYs Quality-Adjusted Life Years

Black line: assumed threshold of €35,000/QALY

Figure 2: Cost-effectiveness acceptability curve



DISCUSSION

Due to a predicted stage shift in breast cancers, namely a reduction of 14.5% in advanced tumors, the screening program was estimated to reduce breast cancer mortality by 14.2% over 20 years. In the Netherlands, a similar reduction in advanced tumours of 12.1% was found after the first eight years of screening program implementation (Fracheboud et al., 2004). Our study showed that biennial mammography screening in Flanders is cost-effective with a probability of 82.9%, regarding a willingness-to-pay of €35,000/QALY. In published literature, studies showing better ICERs were found (Carles et al., 2011; Rojnik et al., 2008), other studies estimated worse ICERs (Mittmann et al., 2015; Pharoah et al., 2013). Making direct comparisons between cost-effectiveness studies is difficult though, since results are dependent on the input data as well as model design. However, some similarities could be recognised in the conceptualisation and results of our study and the study of de Gelder et al. (2009). Their cost-effectiveness study of the Swedish mammography screening program included a realistic participation rate, opportunistic screening and local demographic and epidemiologic data as input parameters for the model. Their study resulted in an ICER of €15,601/QALY gained and a mortality reduction of 13% with 80% biennial mammography screening and 20% opportunistic screening. The number of QALY gained per woman in this study is low; in the current screening program, the gain in QALY is 0.007 per woman aged 50+, which means an extra 3 days. When calculating the QALY gained for the total population cohort, 9,236 QALY (with inflow: 16,532) are gained in case of a screening program compared to no screening program, showing the beneficial impact of BC screening on public health. Beside the benefit in health simulated by our model, the population-based screening program also induced a net cost. The result of the budget impact analysis showed that the screening program generates a net cumulative cost of €492 million for the public health care payer, what can be explained by the screening program inducing more examinations, treatment and follow-up. To compare, the budget impact of the Flemish colorectal cancer screening program was estimated to amount €118 million (Pil, Fobelets, Putman, Trybou, & Annemans, 2016), which shows the financial impact of the BC screening program to be substantial. However, the cost-effectiveness result showed that this invested budget offers value for money. The results of the sensitivity analyses showed the importance of mammograms being performed as scheduled, avoiding waiting times, and consequent costs related to productivity loss. Additionally, the lower the quality of life related to BC stage I, the worse the cost-effectiveness of screening. Screening detects particularly BC stage I lesions, which might never have been detected in case there would be no screening program. The natural progression of BC also highly influences the result. The higher the progression rate, the faster the lesions evolve to a more severe BC state, which favours the screening program. This parameter however is difficult to assess, since no accurate data is available. The annual probabilities were calculated based on the sojourn times described by Tan et al. (Harris & Hellman, 1996; Tan et al., 2013). A higher incidence of undiagnosed BC stage I would result in a better cost-effectiveness of screening, which means that it would be useful to detect subgroups with high incidence rates. It was shown that an increase in participation rate would not influence the ICER to a great extent, illustrating that increase in participation rate should not be the only focus of policy makers. As in most health economic models, the result from a public health care payer (i.e. exclusion of costs due to productivity loss and cost to be paid by the patient) was slightly worse. Screening leads to a

slightly higher cost to the patient (as more tumours are detected and treated), which is compensated for by a high reduction in productivity loss due to prevention of severe tumours. This makes the screening program more interesting from societal perspective in reference to the public health care payer perspective. Extending the time horizon of the model to 50 years ameliorated the ICER to a great extent, as the benefits of screening are taken into account for a longer time period. However, it should be noted that longer time horizons induce more uncertainty (O'Mahony, Newall, & Van Rosmalen, 2015). Despite the change in the incremental cost-effectiveness ratio when simulating different scenarios, all four scenarios resulted in an ICER below the assumed threshold of €35,000/QALY gained. This is the first time that the long term costs and health effects of the BC screening program in Flanders have been evaluated. A major strength of the study is that not only the benefits of BC screening were captured in the model, as in most models (Koleva-Kolarova et al., 2015), but also the negative aspects, such as the mental consequences of a false-positive screening result on quality of life and overdiagnosis, which is implicitly included in the model as all detected tumours were assumed to be treated. However, more research is needed on the negative effects of the screening itself and of a false-positive result on the quality of life, as our analysis showed that this latter parameter affected the cost-effectiveness result. Risk of radiation-induced BCs due to the mammographic screening program was not included in the model, since other studies have shown this risk to be very small. Two studies evaluating the impact of biennial screening from the age of 50 showed a lifetime risk of radiation-induced BC of 0.010% to 0.014% and radiation-induced BC death of 0.0010% to 0.0016% (Hauge, Pedersen, Olerud, Hole, & Hofvind, 2014; Yaffe & Mainprize, 2011). Additionally, productivity loss due to cancer treatment was taken into account in the model. Productivity loss due to the screening test was considered in the sensitivity analysis. The importance of including these costs was shown in the sensitivity analysis since absenteeism due to having a mammography was one of the most influential drivers for the ICER. Furthermore, a budget impact analysis was performed as a part of a comprehensive economic assessment alongside the cost-effectiveness analysis, intended to inform policy makers about the health care expenditure as a consequence of implementing the screening program. Notwithstanding the strengths of our study, it needs to be taken into account that the health benefits of cancer screening due to the stage-shift and mortality reduction as predicted in our model, are still subject of controversy in published literature. Current observational studies provide inconclusive evidence on this predicted stage-shift (Autier et al., 2011; Bleyer & Welch, 2012; de Glas et al., 2014; Lousdal, Kristiansen, Moller, & Stovring, 2014; Weigel, Heindel, Heidrich, Heidinger, & Hense, 2016), so more clinical evidence is necessary to check this prediction. In addition, randomised controlled trials investigating the mortality reduction by systematic screening provide inconsistent results on the mortality reduction due to systematic screening. A Cochrane review reported a mean mortality reduction of 19% (95% CI 13–26%) based on seven trials (10% if only based on the tree optimal trials) (Gotzsche & Jorgensen, 2013), while other researchers believe that early detection by mammography produces no benefit in terms of reduction in mortality and incidence of metastasised tumours (Autier, Boniol, Gavin, & Vatten, 2011; Jorgensen, Zahl, & Gotzsche, 2010; Miller et al., 2014). Besides, some limitations of our study should be addressed. First, the used progression rates were based on tumour size and metastasis since rates on the TNM-staging were not available to our knowledge. Second, including in situ tumours in the

Markov model is a subject of discussion, since not all detected DCIS will progress to a further cancer stage. We decided to include DCIS in the model, although this increased the costs and decreased the quality of life but resulted in a more accurate model of the natural history of BC. Third, this model was an evaluation of the Flemish screening program, based on biennial screening. The model did not allow to compare with other screening frequencies. Although biennial screening has previously been shown to be the most cost-effective option (Rashidian, Barfar, Hosseini, Nosratnejad, & Barooti, 2013), further studies are recommended to evaluate other screening frequencies in the Flemish program such as triennial screening. Finally, it is possible that not all aspects of the impact of breast cancer on the health-related quality of life was incorporated in the QALY-measure, for example sleep deprivation, dignitiy, etcetera. If such aspects would have been captured by the QALY-measure, the cost-effectiveness of screening might have been better.

CONCLUSION

According to the cost-effectiveness threshold of €35,000/QALY, this economic evaluation illustrates the cost-effectiveness of the biennial population-based screening program for BC – with a probability of 82.9%. We should be aware though that the techniques for screening and treatment of cancer are evolving continuously and that population-based screening programs need to be evaluated on a regular basis. Additionally, studies which continue to evaluate the current BC program are necessary to test the predictions made by this model.

APPENDIX

Appendix Table 1: Epidemiological parameters used as input for the prevalence's at start of the model

Model parameter	Input value		
	50-59y	*60-69y*	*70+y*
Prevalence non-identified DCIS	0.06%	0.05%	0.02%
Prevalence non-identified BC stage I	0.16%	0.20%	0.13%
Prevalence non-identified BC stage II	0.11%	0.14%	0.17%
Prevalence non-identified BC stage III	0.04%	0.05%	0.07%
Prevalence non-identified BC stage IV	0.01%	0.02%	0.04%

BC: Breast cancer DCIS: Ductal carcinoma in situ

Source: Prevalences Flanders 2010 (Belgian Cancer Registry, 2010a)

Appendix Table 2: Annual transition probabilities of natural progression

Model parameter	Input value
Progression from DCIS to BC stage I	15%
Progression from BC stage I to BC stage II	27%
Progression from BC stage II to BC stage III	35%
Progression from BC stage III to BC stage IV	55%

BC: Breast cancer DCIS: Ductal carcinoma in situ

Source: based on sojourn times as described in Tan et al. (Harris & Hellman, 1996; Tan et al., 2013)

Appendix Table 3: Risk of metastases in the first 4 years and in long term follow-up

Model parameter	Input value intense FU		Input value long term FU	
	regional	*distant*	*regional*	*distant*
BC stage I	0.26%	1.38%	0.08%	0.43%
BC stage II	0.64%	3.40%	0.20%	1.07%
BC stage III	0.64%	3.40%	0.20%	1.07%
BC stage IV		3.40%		1.07%

BC: Breast cancer

Source: (Siponen, Joensuu, & Leidenius, 2013)

Appendix Table 4: Annual mortality rates

Model parameter		Input value		
		50-59y	***60-69y***	***70+y***
BC-related mortality, year of diagnosis*				
	Stage III	1.40%	2.50%	6.80%
	Stage IV	21.20%	19.30%	32.30%
BC-related mortality, FU year 1-4y*				
	Stage III	3.77%	4.32%	7.59%
	Stage IV	20.48%	21.88%	25.27%
BC-related mortality, FU year 4+y**				
	Stage III	2.58%	2.95%	5.18%
	Stage IV	13.99%	14.94%	17.26%

BC: Breast cancer DCIS: Ductal carcinoma in situ

* Source: Belgian Cancer Registry 2004-2012 (Belgian Cancer Registry, 2014)

** Mortality reduction of 68% 5 years after diagnosis

Appendix Table 5: Medical unit costs in € 2014 price

Model parameter	Input value		
	Health care payer	*Patient (co-payment)*	*Total*
Medical cost diagnosis			
Screening mammography	€ 60	€ 0	€ 60
diagnostic mammography[a]	€ 113	€ 25	€ 138
DCIS	€ 429	€ 45	€ 474
BC stage I	€ 613	€ 64	€ 677
BC stage II	€ 952	€ 100	€ 1,051
BC stage III	€ 1,462	€ 153	€ 1,615
BC stage IV	€ 1,634	€ 172	€ 1,806
Medical cost treatment			
DCIS	€ 4,978	€ 523	€ 5,500
BC stage I	€ 7,111	€ 746	€ 7,858
BC stage II	€ 11,047	€ 1,160	€ 12,206
BC stage III	€ 16,970	€ 1,781	€ 18,752
BC stage IV	€ 18,972	€ 1,992	€ 20,964
Medical cost follow-up (first 4 years after treatment)			
DCIS	€ 524	€ 55	€ 579
BC stage I	€ 749	€ 79	€ 827
BC stage II	€ 1,163	€ 122	€ 1,285
BC stage III	€ 1,787	€ 188	€ 1,974
BC stage IV	€ 1,998	€ 210	€ 2,207

BC: Breast cancer DCIS: Ductal carcinoma in situ

Source: (Broekx et al., 2011)

*Average cost for mammography by radiologist and obstetrician (Rijksinsituut voor Ziekte- en Invaliditeitsverzekering (RIZIV), 2016)

Appendix Table 6: Days off work due to BC treatment or follow-up

Model parameter		Input value
Productivity loss during treatment (days/year)		
	stage I	17
	stage II	25
	stage III	35
	stage IV	55
	DCIS	12
Productivity loss during intense follow-up (days/year)*		
	stage I	7
	stage II	15
	stage III	25
	stage IV	45
	DCIS	2
Productivity loss death**		160

Source: based on estimation of on average 40 days per year in Broekx et al. (Broekx et al., 2011)

*Assumption of 10 days per year less than in the treatment phase

**Source: (Hakkaart-van Roijen, 2010)

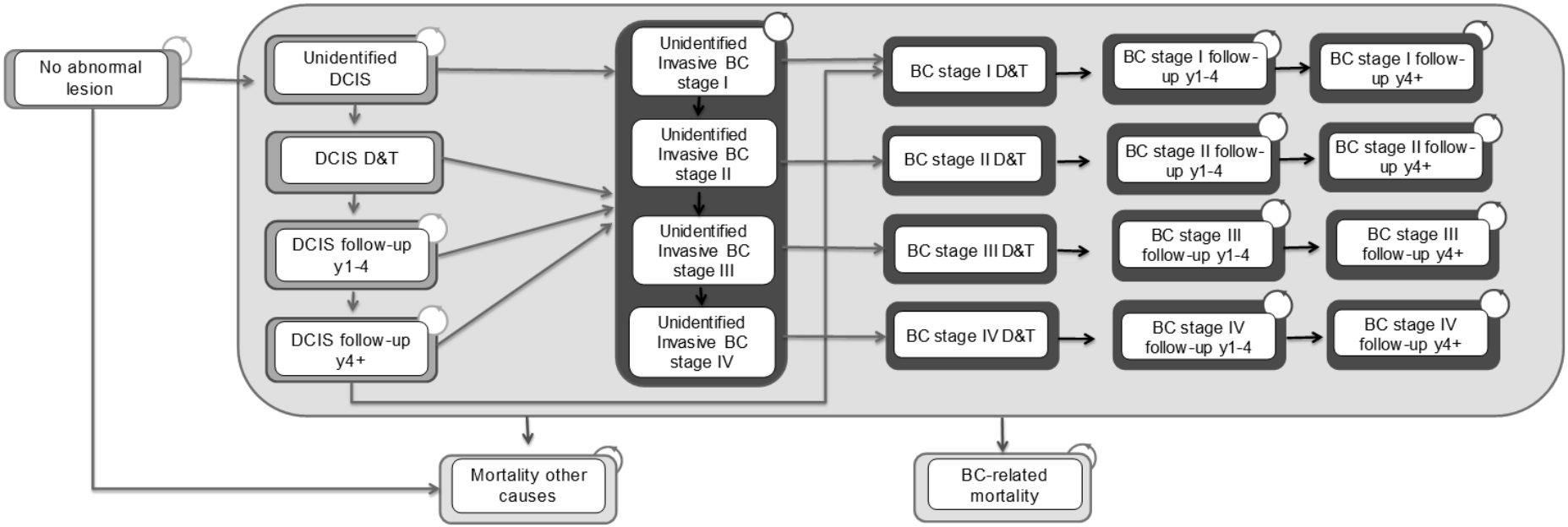
Appendix Table 7: Utilities per BC stage, by age category

Model parameter	Input value		
	50-59y	*60-69y*	*70+y*
No abnormal lesion	0.81	0.793	0.694
False-positive result	0.80	0.79	0.69
DCIS identified	0.72	0.70	0.60
DCIS non-identified	0.77	0.75	0.65
BC stage I identified	0.72	0.70	0.60
BC stage I non-identified	0.77	0.75	0.65
BC stage II identified	0.56	0.54	0.44
BC stage II non-identified	0.69	0.67	0.57
BC stage III identified	0.32	0.30	0.20
BC stage III non-identified	0.57	0.55	0.45
BC stage IV identified	0.19	0.17	0.07
BC stage IV non-identified	0.50	0.48	0.38
Follow-up DCIS*	0.81	0.79	0.69
Follow-up BK I*	0.81	0.79	0.69
Follow-up BK II*	0.74	0.72	0.61
Follow-up BK III*	0.39	0.38	0.32
Follow-up BK IV*	0.21	0.20	0.17

Source: (Kimman et al., 2011; Schleinitz, DePalo, Blume, & Stein, 2006; Scientific Institute of Public Health., 2013)

*Assumption: average utility for follow-up was divided according to stage based on distribution of utility of identified lesions

Appendix Figure 1: Markov model

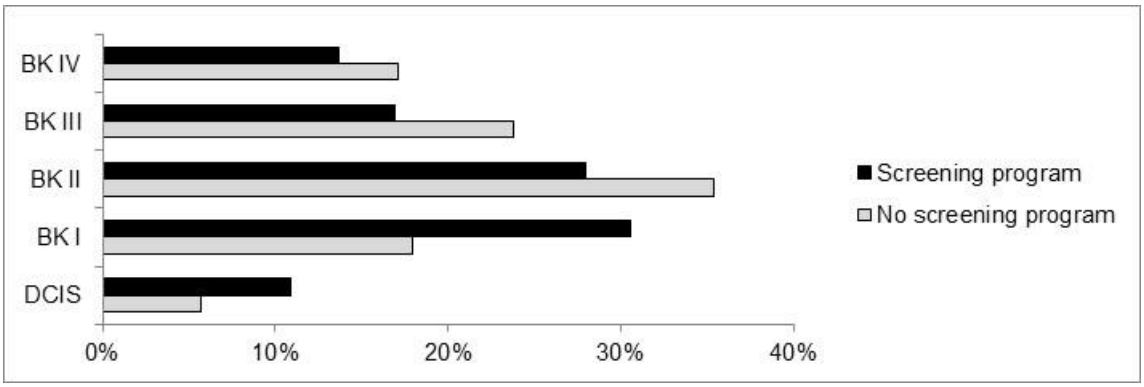


BC = Breast cancer; D&T = diagnosis and treatment; FU = Follow-up.

From the state of treatment or follow-up regional metastasis (Stage III) or distant metastasis (stage IV) can occur, after which one transitions to the treatment phase of this stage.

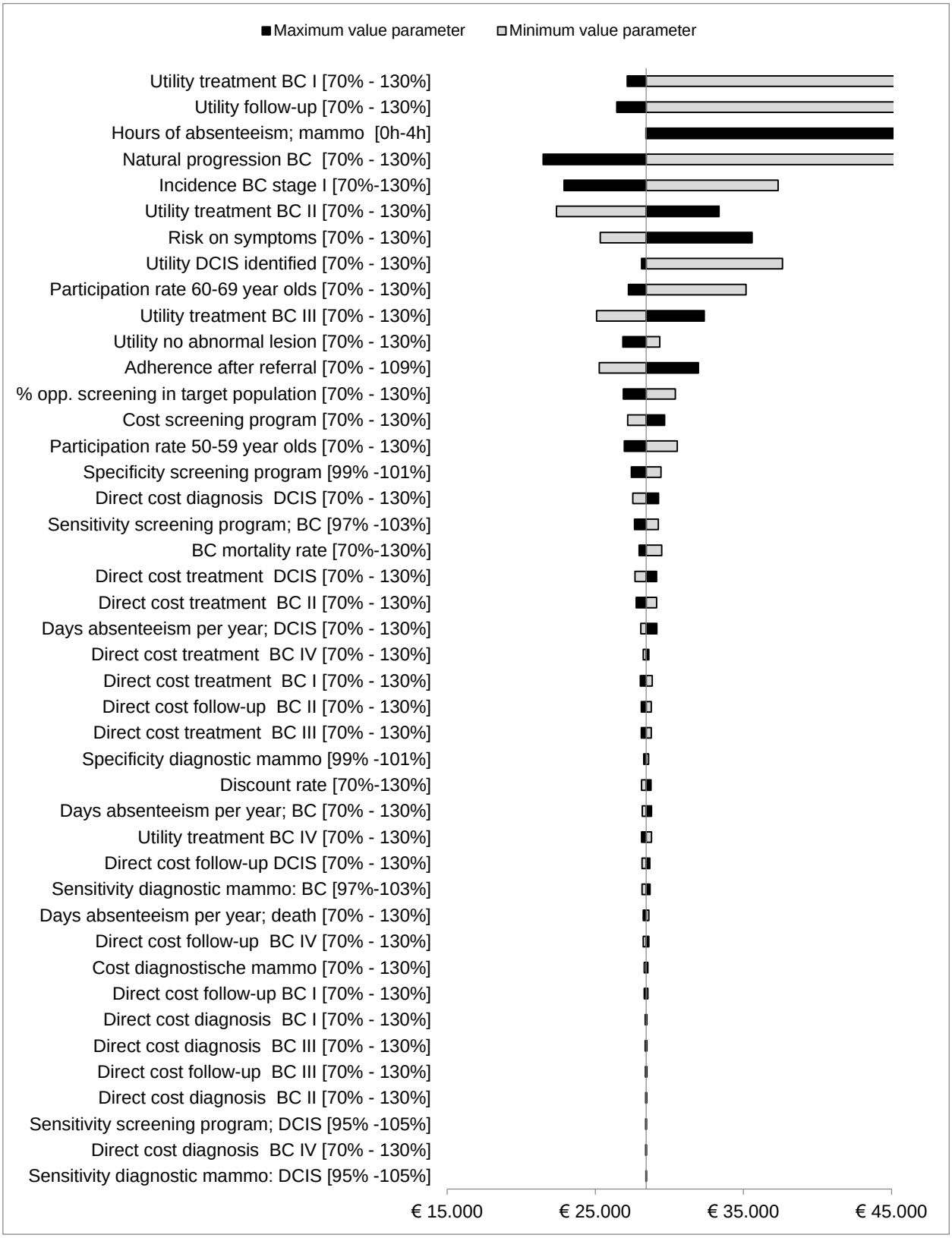
Death from BC is only possible for a person with BC stage III or stage IV.

Appendix Figure 2: Distribution of identified tumours after 20 years in the model, in women aged 50+



BC: Breast cancer DCIS: Ductal carcinoma in situ

Appendix Figure 3: Tornado-diagram showing the results of the one-way sensitivity analysis



Between brackets: range of variation in relative terms

Opp.: Opportunistic BC: Breast cancer DCIS: Ductal carcinoma in situ

2.2.2. Cost-effectiveness and budget impact analysis of a population-based screening program for colorectal cancer

Based on:

Lore Pil, Maaike Fobelets, Koen Putman, Jeroen Trybou & Lieven Annemans. (2016). Cost-effectiveness and budget impact analysis of a population-based screening program for colorectal cancer. *European Journal of Internal Medicine,* 32: 72–78.

ABSTRACT

Background: Colorectal cancer (CRC) is one of the leading causes of cancer mortality in Belgium. In Flanders (Belgium), a population-based screening program with a biennial faecal immunological test (FIT) in women and men aged 56–74 has been organised since 2013. This study assessed the cost-effectiveness and budget impact of the colorectal population-based screening program in Flanders (Belgium).

Methods: A health economic model was conducted, consisting of a decision tree simulating the screening process and a Markov model, with a time horizon of 20 years, simulating natural progression. Mortality and incidence, total costs, and quality-adjusted life-years (QALYs) with and without the screening program were estimated in order to determine the incremental cost-effectiveness ratio of CRC screening. Deterministic and probabilistic sensitivity analyses were conducted, taking into account uncertainty of the model parameters.

Results: Mortality due to CRC and CRC incidence were predicted to decrease over 20 years. Assuming a threshold of €35,000/QALY gained, the colorectal screening program in Flanders was found to be cost-effective with an ICER of €1,582/QALY in males and €3,327/QALY in females. The probability of being cost-effective given a threshold of €35,000/QALY was 100% and 97.3%, respectively. The budget impact analysis showed the extra cost for the health care payer to be limited.

Conclusion: This health economic analysis has shown that despite the possible adverse effects of screening and the extra costs for the health care payer and the patient, the population-based screening program for CRC in Flanders is cost-effective and should therefore be maintained.

INTRODUCTION

Colorectal cancer (CRC) is the fifth leading cause of death in Europe. From a national perspective, it is the third most prevalent cancer in Belgian men and the second most prevalent cancer in Belgian women (Stichting Tegen Kanker, 2015b). Annually, 8500 people in Belgium are diagnosed with CRC (Stichting Tegen Kanker, 2015a) and about 3000 persons die from the disease. In light of this burden, program-based cancer screening has been recommended by various international organisations (European Commission, 2010a; U.S.Preventive Services Task Force, 2008; Von Karsa et al., 2003). However, in times of limited budgets, policymakers require clinical and health-economic evidence in order to spend the available resources in the most optimal way. Several studies have illustrated that detection of pre-cancerous lesions (adenomas) and early-stage cancers results in significant health benefits, although observational studies provide inconsistent results on the magnitude of these benefits (Faivre et al., 2004; Hardcastle et al., 1996; Kronborg, Fenger, Olsen, Jorgensen, & Sondergaard, 1996; Ventura et al., 2014; Zorzi et al., 2015). The CRC screening policy recommended by the European Commission is the Faecal Occult Blood test for men and women aged 50-74 with a screening interval of maximum 2 years (European Commission, 2010a). Since 2013, a biennial CRC population-based screening program has been organised in Flanders, the northern region of Belgium, inviting men and women between 56 and 74 years old to be screened by means of the faecal immunological test (FIT). The FIT seems to be a cost-effective alternative to the older and low-sensitivity Guaiac Faecal Occult Blood test (Sharp et al., 2012; Telford, Levy, Sambrook, Zou, & Enns, 2010). However, up to now, the value for money of the recent Flemish CRC screening program has not yet been evaluated. Therefore, the purpose of this study was to analyse the cost-effectiveness as well as the budget impact of the population-based CRC screening program in Flanders. The result of this analysis is an important source of information for policy makers in order to make evidence-based choices concerning the screening policy for CRC.

METHODS

Screening strategy

The health economic model assessed the costs and effects of the Flemish CRC screening program and compared these costs and effects to those expected in the absence of an organised screening program. In the Flemish CRC screening program a FIT is mailed to the target population as a self-test with simple instructions. The stool needs to be pierced with a small included stick and mailed back for testing. The stool is then analysed by means of the one-sample OC-sensor test[13], using a haemoglobin cut-off value of 75 nanogram/millilitre. At each FIT-screening round, men and women attending the screening may have either a (false) negative result or a (false) positive result which will lead to further examination with colonoscopy. After a negative colonoscopy, one is not invited to the screening program for the next 10 years. After a positive colonoscopy, the patient is treated accordingly.

[13] The OC-sensor test (Eiken) is a quantitative immunological fecal occult blood test, an automated analyzer testing the hemoglobin in stool samples.

General model description

The health economic model consisted of a decision tree, simulating the screening process, and a state-transitional Markov model simulating the natural progression of the disease, over a period of 20 years, for the Flemish population aged 50 and older. The population was distributed in age-categories of five years and simulated until they reached the age of 100 or until death. Several disease states were comprised in the model, categorised as unidentified lesions (i.e. not yet detected and diagnosed by a physician) and identified lesions (i.e. detected and diagnosed) (Figure 1). At the start of the model, according to observed 2011 prevalence figures and the screening yield, the total population was distributed over the state of 'free of any abnormal lesion', 'unidentified polyp' (defined as non-adenomatous polyp, low-risk adenomatous polyp[14] or high-risk adenomatous polyp), or 'unidentified invasive CRC', assuming that all existing lesions were unidentified by start. Furthermore, the model presumed all cancers to arise from pre-existing adenomas. Adenomas could only be detected by means of organised or spontaneous screening since it was assumed that these lesions are not associated with symptoms. Non-adenomatous and low-risk adenomatous polyps could naturally regress every year. However, all polyps detected by screening were removed by polypectomy (resection). CRC stages were determined according to the 7th edition of the Tumour-Nodes-Metastases classification for malignant tumours (Sobin et al., 2009). The population transitioned through the states on an annual basis, based on age- and gender-specific transition probabilities estimated from national epidemiologic data and published literature. From the stages treatment or follow-up, one could develop regional metastases (stage III) or distant metastases (stage IV) and go back into treatment. From stage III and stage IV, one could die from CRC and from all stages one could die from other causes than CRC. CRC could be detected by means of the screening program, spontaneous opportunistic screening in case one was not invited or did not participate in the screening program, or it could be clinically detected (based on symptoms). In case of detection, in either way, it was assumed that the tumour was treated in the same year of detection. In the year following treatment, the patient progressed to the follow-up state which was separated into a temporary intense follow-up state (first 4 years) and a long term follow-up state (next years), because of more intense follow-up due to a higher risk of death in the first years after treatment.

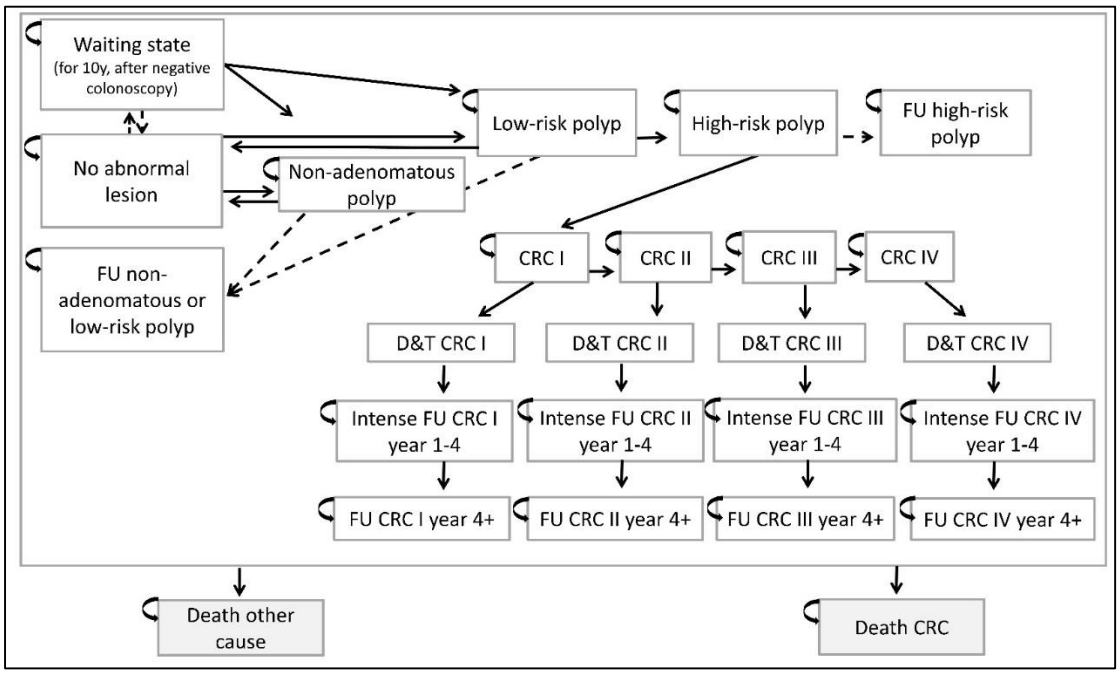
Epidemiological and clinical inputs

Epidemiologic input data were collected from the Belgian Cancer Registry. The prevalence of unidentified CRC at start of the model was defined as the total prevalence of CRC, namely, the prevalence of registered CRC diagnoses (most recent available data, but before the screening program was implemented) (Belgian Cancer Registry, 2010b), supplemented with the yield of the screening program (2014). Since at the moment of the analysis, test characteristics of the screening were not yet systematically measured, we relied on published literature to estimate the sensitivity and specificity of the FIT and colonoscopy. The incidence of polyps was derived from the study of Brenner et al. (2014), as diagnosis of polyps is not registered in Belgium. However, a correction factor to the Belgian situation was applied, based on CRC incidence of both countries (GLOBOCAN, 2012). Prevalence at start of the

[14] 1 or 2 small tubular adenomatous polyps with low-grade dysplasia; serrated polyps <10mm or without dysplasia

model and transition probabilities between the disease states are depicted in the Appendix Table A1-A4. All screening-related data were obtained from the Flemish government (Centrum voor Kankeropsporing, 2013) (Table 1). Annual constant screening uptake rates were applied over the years, meaning that participation was not linked to disease incidence or progression.

Figure 1: Markov model depicting the natural progression of CRC and the possible transitions.



CRC = colorectal cancer; D&T = diagnosis and treatment; FU = Follow-up.

From the state of treatment or follow-up regional metastasis (stage III) or distant metastasis (stage IV) can occur, after which one transitions to the treatment phase of this stage. Death from CRC is only possible for a person with CRC stage III or stage IV. Dotted lines correspond to transitions which are only possible in case of systematic or opportunistic screening.

Health-economic inputs

Health effects of the screening program are represented as the impact on CRC mortality and on the quality of life of patients. The combination of these effects is expressed as quality-adjusted life-years (QALY), calculated by means of (EQ-5D index) utilities during the lifespan of the model population. Utilities express the quality of life with a value between 0 (death) and 1 (perfect health). The utilities used in the model are age- and gender-specific and were derived from Flemish as well as international published data (Appendix Table 5). A false-positive FIT result was assumed to be associated with a utility loss of 10% for three months in reference to the general population utility, because of the related psychological stress (Cullen, Schwartz, Lawrence, Selby, & Mandelblatt, 2004). The utility for patients in follow-up was calculated as the average of the utility for patients with a detected tumour and patients with an undetected tumour.

The cost-effectiveness analysis was conducted from a societal perspective, including direct medical as well as indirect costs due to productivity loss because of morbidity, or premature death. All costs in the model were calculated in euro with 2014 as reference year. Medical costs were separated into costs for detection and diagnosis, costs for treatment, and costs for follow-up. The medical costs for detection

and diagnosis were calculated per stage based on official Belgian costs of medical procedures. The medical costs for treatment and for follow-up were derived from the Belgian report of Pacolet et al. (2011) and made stage-specific based on the ratios of the study of Tilson et al. (2012). For the treatment cost of stage IV, a correction was applied to take into account the new and more expensive therapies (panitumumab, cetuximab) that emerged in the last few years.

Cost due to productivity loss were estimated according to the friction cost method (Hakkaart-van Roijen, 2010). The number of days off work were multiplied by the cost for one day absenteeism estimated previously by the Belgian Health Care Knowledge Centre (Cleemput et al., 2012). A productivity loss of 160 days was assigned to deceased people (Hakkaart-van Roijen, 2010). These costs due to productivity loss were only applied to the productive age-categories of 50-65 years, taking into account the proportion fulltime equivalents and the unemployment rate. Future costs were discounted with 3% and health effects with 1.5%, according to the Belgian guidelines for health economic analyses (Cleemput et al., 2012). Appendix Table 6 shows the costs for diagnosis, treatment, and follow-up.

Table 1: Screening-related parameters

Model parameter	Input value					
	56-60y		*61-70y*		*71-74y*	
	males	*females*	*males*	*females*	*males*	*females*
Participation rate screening*	43.90%	43.10%	51.20%	50.20%	45.30%	44.50%
Adherence to colonoscopy (after positive FIT)*	82.20%	82.20%	95.80%	95.80%	84.80%	84.80%
% of screening population with spontaneous opportunistic screening*	6.17%	7.21%	6.34%	6.93%	5.53%	5.94%
Sensitivity screening FIT for polyps and low-risk adenomas**	5.70%					
Sensitivity screening FIT for polyps and high-risk adenomas**	34.20%					
Sensitivity screening FIT for CRC**	73.00%					
Specificity screening program**	97.00%					

CRC: colorectal cancer DCIS: ductal carcinoma in situ

*Source: Annual report Flemish cancer screening, 2013 (Centrum voor Kankeropsporing, 2013)

** Source: (Goede et al., 2013; Kovarova et al., 2012; Wilschut et al., 2011)

Outcome parameters

Over a period of 20 years, the difference in total costs was divided by the difference in total effects resulting in an incremental cost- effectiveness ratio expressed as a cost per QALY gained. The budget impact analysis measured the net cumulative cost of the screening program for the public health care payer (including the cost of consequent examinations, treatment, and follow-up) over a period of 20 years. To calculate the budget impact, an annual inflow of new 50-year-old persons was assumed. As

shown by previous studies, CRC screening is expected to result in a decrease in the incidence and mortality of CRC. Both were calculated as the difference between the invited and non-invited cohort.

Scenario and sensitivity analyses

Several additional scenarios were tested. In the first scenario, 50- to 55-year olds were included in the screening program as recommended by the European guidelines (European Commission, 2010a). In the second scenario the costs for the patient and the costs due to productivity loss were excluded (i.e. public health care payer perspective) and in the third scenario the minimum value of the utility in case of a false-positive result was set to the utility of CRC stage I in treatment and the maximum value to the utility of no abnormal lesion (worst case – best case). In a final scenario the time horizon of the model was extended to 50 years instead of 20 years. In the scenario with a time horizon of 50 years, an annual inflow of new 50-year olds was included, as after 20 years the original cohort is not eligible for screening anymore. Both one-way and probabilistic sensitivity analyses were conducted to take into account uncertainty in the input parameters and to test the robustness of the results. The one-way sensitivity analysis included the cost of the screening program, medical costs, days off work, utilities, test characteristics of the FIT and colonoscopy, participation rate per age-category, percentage performed colonoscopies after referral, prevalence of non-identified polyps, incidence of low-risk adenomatous polyps, positivity rate of the screening program, natural progression rates, mortality rates and the discount rate. These parameters were varied based on standard error estimates or based on ±30% ranges in case standard errors were not available. In order to perform the probabilistic sensitivity analysis (PSA), probability distributions were defined for the costs (gamma distribution), utilities (beta distribution), test characteristics of the FIT and colonoscopy (beta distribution), prevalence and incidence of low-risk adenomatous polyps (beta distribution), participation rate per age-category (beta distribution), and days off work (normal distribution). A cost-effectiveness plane was plotted to visualise the values of the 5000 2nd-order Monte Carlo simulations. As to provide information on the proportion of simulations with a cost-effective result, given a certain willingness-to-pay threshold, a cost-effectiveness acceptability curve (CEAC) was drawn.

RESULTS

Base case

Over a period of 20 years, the screening program is expected to reduce CRC mortality by 23% in males and 19% in females and the incidence of invasive CRC (i.e. stage III-IV) by 26.6% in males and 21.5% in females. In the first years of the model, more tumours were detected in persons invited for screening than in controls, while in later years, more tumours were found in the control cohort (Appendix Figure 1). Additionally, 0.012 QALY were gained per male aged 50+ and 0.005 QALY per female aged 50+, against an incremental cost of €19 and €18, respectively. The incremental cost-effectiveness ratio of the CRC screening program, in reference to no screening program, was €1,582/QALY in males and €3,327/QALY in females (Table 2). Over a period of 20 years, the screening program resulted in a net cumulative cost of €63,084,518 in males, and €54,528,777 in females, totaling the extra cost over 20 years to €117,613,295 (Table 3), or €5 per year per person in the target group (56-74y).

Table 2: Results of the cost-effectiveness analysis, with several scenarios

Scenario	Δ cost (€)		Δ QALY		ICER (€/QALY)		Mortality reduction	
	males	**females**	**males**	**females**	**males**	**females**	**males**	**females**
Base case det.	19	18	0.012	0.005	1,582	3,327	23%	19%
Public health care payer perspective	32	24	0.012	0.005	2,666	4,800	23%	19%
Incl. 50-55 year olds	16	18	0.013	0.006	1,211	3,169	25%	20%
Utility false positive: best case	19	18	0.013	0.006	1,444	2,860	22%	19%
Utility false positive: worst case	19	18	0.005	-0.002	4,212	negative	22%	19%
Time horizon 50 year	-1596	-70	0.070	0.033	cost-saving		25%	20%
Base case prob.	17	16	0.011	0.005	1,681	4,484	20%	19%
(95% CI)	(-15 – 57)	(-5 – 48)	(0.007 – 0.014)	(0.001 – 0.007)	(-1,317 – 6,601)	(-3,254 – 18,163)	(16% – 23%)	(15% – 22%)

Δ cost: total cost with screening program minus total cost without screening program.

Δ QALY: total QALY with screening program minus total QALY without screening program.

ICER: Incremental cost-effectiveness ratio.

Mortality reduction: mortality due to CRC without screening program (i.e. non-invited) minus with screening program (i.e. invited). det.: deterministic prob.: probabilistic.

Table 3: Results of the budget impact analysis

	Cost health care payer	Cost for organisation of screening	Total extra cost
males			
With screening program	€ 1,046,716,220	€ 28,901,310	**€ 63,084,518**
Without screening program	€ 1,012,533,012	€ 0	
females			
With screening program	€ 787,561,407	€ 29,235,862	**€ 54,528,777**
Without screening program	€ 762,268,492	€ 0	

Scenario and sensitivity analyses

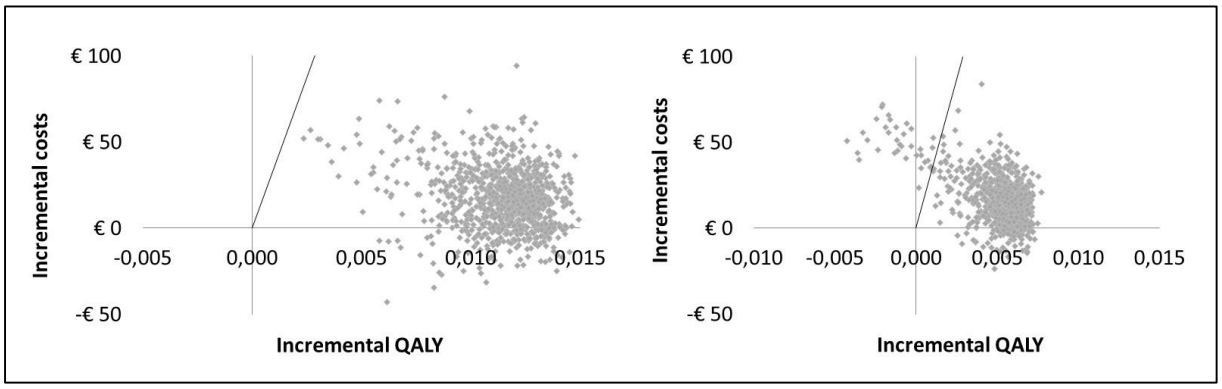
Results of the different scenarios are shown in Table 2. When opting to invite 50- to 55-year olds to the screening program (in line with the European guidelines but not currently implemented), there was only a marginal increase in net QALYs and decrease in net costs, resulting in a slightly better ICER. Excluding costs due to productivity loss worsened the result to a small extent. The worst scenario was found if the quality of life in females in case of a false-positive would be similar to that in case of diagnosis and treatment for CRC stage I. Then the positive effect of screening on the quality of life would be overshadowed by the negative effect. Extending the time horizon to 50 years instead of 20 years -including annual inflow- altered the outcome markedly as the result became cost-saving. All scenarios were in favour of the CRC screening program.

Results of the one-way sensitivity analysis present the influence of the parameters on the cost-effectiveness result. The parameters with the highest impact were the sensitivity of the FIT for high-risk polyps, the natural progression of CRC, the risk on symptoms, the specificity of the FIT, the prevalence of unidentified high-risk polyps, the adherence to colonoscopy after referral, and the sensitivity of colonoscopy for high-risk polyps. When the value of these parameters was varied to the maximum, then the incremental cost-effectiveness ratio ameliorated, except for the risk on symptoms. Consequently, the opposite was true when the value of these parameters was varied to the minimum. Importantly, in all simulations, the result remained cost-effective, demonstrating the robustness of the result in the base case scenario. A change in the participation rate -one of the main features of a screening program- did not considerably influence the result. Tornado diagrams are shown in Appendix Figure 2.

A PSA with 5,000 Monte Carlo simulations was performed, generating credibility intervals (CI) around the point estimate of the ICER. Over a period of 20 years, the PSA resulted in an incremental cost-effectiveness ratio of €1,681/QALY (95% CI €-1,317 to €6,601/QALY) in males and €4,484/QALY (95% CI €- 3,254 to €18,163/QALY) in females (Table 2). The cost-effectiveness planes display the result of the simulations (Figure 2). Most of the simulations were situated in the north-east quadrant of the graph, meaning that the screening program resulted in health benefits but against an extra cost, as shown by the cost-effectiveness results. In the analysis for males all points and in the analysis for females almost all points are situated below the willingness-to-pay threshold of €35,000/QALY gained which shows the

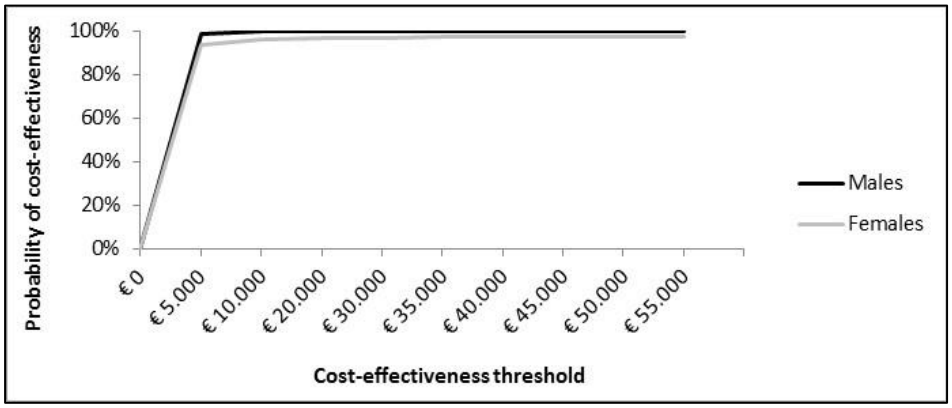
robustness of the result being cost-effective. In some of the simulations, the screening program was expected to result in health benefits and cost-savings (south-east quadrant). However, in females, some simulations also resulted in a loss of health benefits due to the screening program (north-west quadrant). The CEAC (Figure 3) depicts the probability for the biennial FIT to be cost- effective in case of a willingness-to-pay threshold ranging from €5,000 to €55,000/QALY. The Flemish CRC population-based screening program has a probability of 100% and 97.3% to be cost-effective in males and females, respectively, given a threshold of €35,000/QALY.

Figure 2: cost-effectiveness plan for males (left) and females (right)



Black line: willingness-to-pay threshold of €35,000/QALY gained

Figure 3: Cost-effectiveness acceptability curve



Model validation

Results of the health economic analysis were internally validated with respect to the observed results from the actual screening program. Estimated average positivity rates derived by the model were lower than field results (5% versus 10%). Two arguments can be proposed. First, the prevalence and incidence of polyps is uncertain. These input figures could be underestimated in the model, leading to lower estimated positivity rates. Second, the test-characteristics of the FIT were not derived from the Flemish screening program as they are not available yet. It could be that the test-characteristics used in the model, differ from the ones in the screening program. However, we chose not to calibrate the parameters based on these results as the observed positivity rate of 10% is the one observed in the first screening round only. It is expected that future screening rounds will result in a lower yield. Moreover, the first screening round only included people aged over 66 years, while in the model, people aged 56-66 years were also invited. To compare, the pilot screening study in one Flemish province in 2009 had a positivity rate of 5.3%, and also the study of Hol et al. (2009) - using the same FIT and hemoglobin cut-off value—showed a positivity rate of 5.7% in the Dutch trial, which are both closer to our estimations. The false-positive rate in the actual screening program was not determined yet at the time of this analysis. We calculated a false-positive rate of the FIT of on average 2.2%. Besides, the distribution of the cancer prevalence according to the stage over 20 years in the absence of the screening program was compared to the stage distribution of tumours in 2010 (Belgian Cancer Registry, 2010b). These were 25%, 31%, 29% and 15% from stage I tot IV in the model, and 21%, 32%, 30% en 17% in real-life, showing the predicted distribution to approximate the observed.

DISCUSSION

The health economic evaluation showed that the Flemish population-based CRC screening program with a biennial FIT is highly cost-effective, considering a threshold of €35,000/QALY gained. These results are in concordance with studies from other countries (Hassan et al., 2011; Heresbach, Chauvin, Grolier, & Josselin, 2010; Lejeune, Dancourt, Arveux, Bonithon-Kopp, & Faivre, 2010; Sharp et al., 2012; Wilschut et al., 2011), although these studies may have included different values for the screening parameters such as for participation rate or other parameters. Consequently, the use of different methodologic approaches and different model designs to assess the cost-effectiveness ratios, makes study results difficult to compare directly. In our analysis, the population-based CRC screening program yielded a rather small number of QALYs per person, but when interpreted on the population level, it leads to a considerable benefit for the Flemish population aged over 50 years of 20,451 QALYs (or with inflow: 26,047 QALYs). This health benefit is higher than in the Flemish BC screening program (Fobelets M*, Pil L*, Putman K, & Annemans L, 2016). The gain in QALYs is a reflection of the predicted decrease in incidence and mortality of CRC. This argues for the early detection and treatment of polyps (and tumours) leading to aversion of new and more advanced CRC tumours. However, it must be taken into account that these findings were not yet proven by randomised controlled trials (RCTs) or observational studies, as the screening program is only been running from 2013. Hewitson et al. (2007) evaluated in their meta-analysis the combined results from three RCTs that used biennial screening with the Guaiac Faecal Occult Blood test and showed a 15% mortality reduction (RR 0.85, CI: 0.78-0.92) with an average

follow-up of 17 years and an average participation rate of 61%. As the sensitivity of the FIT is shown to be better compared to the Guaiac Faecal Occult Blood test (Brenner & Tao, 2013; Guittet et al., 2007), it is expected that the reduction in CRC incidence and mortality due to FIT will be higher. Few observational studies up to now have evaluated these FIT health benefits though. Ventura et al. (2014) showed a mortality reduction of 41% over a period of 11 years (with 40% participation). However, these results are calculated for invited participants versus invited non-participants, while in our study an invited cohort (with an average participation rate of 44%) was compared to a non-invited cohort, which makes comparison with the results of Ventura et al. difficult. Comparing screened persons versus non-screened persons should indeed show better results, as in Ventura et al. Another recent Italian study showed a mortality reduction of 24% over 16 years (with participation of about 50%) (Zorzi et al., 2015). This result is better than the expectations based on our model. However, based on the few available observational studies evaluating FIT today, it is difficult to validate the predictions of our model yet. More real-life evidence is necessary. However, the CRC population-based screening program was predicted not only to result in a health gain but also to induce a net cost. The result of the budget impact analysis showed that over 20 years, the screening program would lead to a net cumulative cost of €118 million for the government. It can be deducted that the screening program induces more examinations, treatment, and follow-up, leading to higher costs for the health care payer. However, the cost-effectiveness result showed that this invested budget offers value for money. Besides, compared to the total extra cost due to the BC screening program (€492 million), the budget impact can be assessed as limited (Fobelets M* et al., 2016). The cost-effectiveness result in our analysis was better for males than for females, which can be explained by the higher prevalence of non-identified polyps and CRC tumours at the start of the model and higher incidence of polyps in males than in females. Hence, screening can attain a greater benefit in males in terms of earlier detection and treatment and mortality reduction. The more favourable result by introducing the age-category 50-55 in the screening program could be explained by the fact that when a tumour is detected early in these persons, more healthy life-years could be gained since persons in this age-category have a higher average quality of life than older persons. Extending the time horizon to 50 years instead of 20 years altered the cost-effectiveness result quite markedly. Over a period of 50 years the CRC screening program would be cost-saving. The one-way- and probabilistic sensitivity analyses demonstrated the test-characteristics of the FIT, the natural progression of CRC, the risk on symptoms, the prevalence of high-risk polyps and patient adherence to be the most influencing parameters, although the conclusion based on the cost-effectiveness result remains the same. The Flemish CRC population-based screening program has a probability of 100% and 99.6% to be cost-effective in males and females respectively.

It is the first time that both costs and benefits of the CRC screening program in Flanders have been analysed thoroughly. Not only the benefits of screening were captured in the model but since there has been a lot of debate concerning the negative aspects of population-based screening, we have tried to include the impact of a false-positive screening result on quality of life in terms of psychological harms as well. However, anxiety that could possibly be induced by receiving the mailing kit and by participating in the screening, regardless of the test result, was not included since we are not able to estimate this parameter because of the lack of scientific evidence. The risk of overtreatment was implicitly included

in the model. Polyps that are detected are removed at the same time, by means of polypectomy, regardless of whether this polyp would have caused any harm. These costs are included in the model. Direct costs related to colorectal cancer, used in our model, were derived from the study of Pacolet et al. (2011), and were based on the 'All Patient Refined-Diagnostic Related Groups'-classification. The basis for this classification consists of the main diagnosis in combination with surgery procedures, the age and sex of the patient, and occurrence of complications. This means that the cost associated with the risk of bowel perforation or bleeding as a consequence of colonoscopy, is implied in the cost estimates.

Nonetheless, some limitations of our analysis should be addressed. First, the incidence and prevalence of adenoma is uncertain, since these data are not registered in the Belgian cancer registry. For the adenoma incidence we had to rely on data from the German screening colposcopy register as provided by Brenner et al. (2014). A correction was applied in reference to the ratio between CRC incidence in Germany and in Belgium. However, in case of multiple adenoma only the largest was recorded, which results in an underestimated incidence rate. Moreover, the prevalence of adenoma identified in the opportunistic circuit in Belgium is unknown so we could only rely on the number of adenoma identified in the screening program (2014). These shortcomings possibly resulted in an underestimation of the incidence and prevalence of adenoma and thus an underestimation of the yield of the screening program. Consequently, the result of our analysis is rather a conservative estimate of the cost-effectiveness ratio. Second, evidence about the test-characteristics of the FIT and colonoscopy in the Flemish population is not available yet as the screening program has only been implemented since October 2013. Therefore, numbers from published literature were used. One-way sensitivity analysis showed the test-characteristics of the FIT to have the highest influence on the cost-effectiveness result. This should be kept in mind when interpreting the results. We used published test-characteristics, but information on the test-characteristics of the screening program should be available soon. Third, due to a lack of information on the natural progression of CRC, these progression rates had to be derived from U.S. studies which estimated these rates based on calibration to observed data (Hur, Chung, Schoen, & Gazelle, 2007; Pickhardt et al., 2007). Fourth, all CRC were assumed to arise from a prior adenoma. In reality, although negligible, there is a small percentage of CRC tumours that do not arise from a pre-existing adenoma. Fifth, separate analyses for low-SES subgroups were not performed in this study. In these subgroups, CRC mortality is expected to be higher, although CRC incidence might be lower (Manser & Bauerfeind, 2014). This difference in epidemiology, together with a predicted lower screening uptake, can influence the cost-effectiveness of CRC screening in these groups. Lastly, it should be noted that screening parameters such as participation rate as well as unit costs of detection, treatment, and follow-up are context-specific limiting the direct transferability of the results across different countries. However, we believe that this positive health economic evaluation can inspire policy makers internationally and stimulate them to make similar evaluations.

CONCLUSION

In this health economic analysis, the cost-effectiveness and budget impact of the population-based CRC screening program in Flanders was evaluated. Results of the analysis show that, despite the possible adverse effects of screening, and the induced costs for the health care payer and patient, the population-based screening program for CRC in Flanders is very cost-effective and should be maintained. Policymakers could decide to also include 50- to 55-year-old males and females in accordance to the European guidelines. Although there is currently few long term real-life evidence on the effectiveness of FIT in terms of reduction in CRC incidence and -mortality, modelling should be used to estimate the cost-effectiveness of a screening program and the potential impact of changes in policy. Additionally, we should be aware that the techniques for screening and treatment of cancer are evolving continuously, emphasising the need to frequently evaluate the population-based screening programs.

APPENDIX

Appendix Table 1: Epidemiological parameters used as input for the prevalence at start of the model

Model parameter		Input value				
		50-55y	*56-59y*	*60-69y*	*70-74y*	*74+*
prevalence non-identified non-adenomatous polyps *	males	2.95%	2.95%	3.80%	4.40%	4.50%
	females	1.60%	1.60%	2.10%	2.70%	3.30%
prevalence non-identified low-risk polyps*	males	3.90%	3.90%	4.98%	5.80%	6.01%
	females	2.10%	2.10%	2.80%	3.58%	4.31%
prevalence non-identified high-risk polyps*	males	2.00%	2.00%	2.56%	2.97%	3.08%
	females	1.08%	1.08%	1.43%	1.84%	2.21%
prevalence non-identified CRC Stage I*/**	males	0.25%	0.28%	0.61%	0.33%	0.84%
	females	0.11%	0.11%	0.27%	0.20%	0.60%
prevalence non-identified CRC Stage I*/**	males	0.12%	0.14%	0.42%	0.23%	0.76%
	females	0.04%	0.06%	0.16%	0.14%	0.60%
prevalence non-identified CRC Stage II*/**	males	0.10%	0.13%	0.31%	0.23%	0.52%
	females	0.05%	0.08%	0.23%	0.15%	0.48%
prevalence non-identified CRC Stage IV*/**	males	0.07%	0.08%	0.24%	0.10%	0.26%
	females	0.02%	0.05%	0.18%	0.10%	0.19%

* Derived from yield screening program, 2014

** Prevalence Flanders 2010 (Belgian Cancer Registry, 2010b) + yield screening program 2014

Appendix Table 2: Annual transition probabilities of natural progression

Model parameter		Input value				
		50-55y	***56-59y***	***60-69y***	***70-74y***	***74+***
Annual risk to develop non-adenomatous polyps[1]	males	1.74%	1.67%	1.74%	1.59%	1.30%
	females	1.01%	1.09%	1.16%	1.16%	0.87%
Annual risk to develop low-risk polyps[1]	males	2.40%	2.30%	2.40%	2.20%	1.80%
	females	1.40%	1.50%	1.60%	1.60%	1.20%
Progression from low- to high-risk polyps[2]	males	4.24%	4.00%	4.00%	4.10%	3.70%
	females	4.00%	3.60%	3.70%	4.70%	3.70%
Progression from high-risk polyp to CRC stage I[2]	males	2.60%	3.10%	3.80%	5.10%	5.20%
	females	2.50%	2.70%	3.80%	5.00%	5.60%
Progression from CRC stage I to CRC stage II[3]	males	30.00%	30.00%	30.00%	30.00%	30.00%
	females	30.00%	30.00%	30.00%	30.00%	30.00%
Progression from CRC stage II to CRC stage III[4]	males	45.00%	45.00%	45.00%	45.00%	45.00%
	females	45.00%	45.00%	45.00%	45.00%	45.00%
Progression from CRC stage III to CRC stage IV[4]	males	50.00%	50.00%	50.00%	50.00%	50.00%
	females	50.00%	50.00%	50.00%	50.00%	50.00%
Natural regression of non-adenomatous and low-risk polyps[5]	males	2.00%	2.00%	2.00%	2.00%	2.00%
	females	2.00%	2.00%	2.00%	2.00%	2.00%

CRC: colorectal cancer

1 (Brenner, Altenhofen, Stock, & Hoffmeister, 2014) 2 (Brenner et al., 2007) 3 (Pickhardt et al., 2007) 4 (Hur et al., 2007) 5 Expert opinion dr. Luc Colemont

Appendix Table 3: Annual mortality rates

	Year of diagnosis*	FU year 1-4*	FU year 4+ **
CRC Stage III			
males	11.60%	7.60%	5.20%
females	12.50%	7.90%	5.40%
CRC Stage IV			
males	37.10%	30.60%	20.90%
females	41.70%	31.70%	21.60%

* (Belgian Cancer Registry, 2014)

** Assumption: Same trend in mortality risk after 5y as described for breast cancer (Early Breast Cancer Trialists' Collaborative Group (EBCTCG)., 2005), i.e. from year 5 on, mortality risk is one third lower than in first follow-up years.

Appendix Table 4: Risk of metastases in the first 4 years and in long term follow-up

	Input value intense FU		Input value long term FU	
	regional	*distant*	*regional*	*distant*
CRC stage I	0.67%	0.89%	0.21%	0.28%
CRC stage II	1.42%	3.12%	0.44%	0.98%
CRC stage III	1.81%	7.04%	0.56%	2.20%
CRC stage IV		29.57%		9.26%

Appendix Table 5: Utilities

Model parameter	**Input value**									
	Males					***Females***				
	50-54j	*55-56j*	*60-69j*	*70-74j*	*75+*	*50-54j*	*55-56j*	*60-69j*	*70-74j*	*75+*
No abnormal lesion*	0.86	0.83	0.84	0.86	0.75	0.82	0.81	0.80	0.79	0.67
False-positive result**	0.84	0.81	0.82	0.84	0.73	0.80	0.79	0.78	0.77	0.65
Non-identified adenoma***	0.78	0.74	0.76	0.77	0.66	0.73	0.72	0.71	0.70	0.58
Identified adenoma***	0.78	0.74	0.76	0.77	0.66	0.73	0.72	0.71	0.70	0.58
CRC stage I non-identified***	0.78	0.74	0.76	0.77	0.66	0.73	0.72	0.71	0.70	0.58
CRC stage I identified***	0.69	0.66	0.67	0.69	0.69	0.65	0.64	0.63	0.62	0.50
CRC stage II non-identified***	0.78	0.74	0.76	0.77	0.66	0.73	0.72	0.71	0.70	0.58
CRC stage II identified ***	0.69	0.66	0.67	0.69	0.69	0.65	0.64	0.63	0.62	0.50
CRC stage III non-identified***	0.72	0.69	0.70	0.72	0.72	0.68	0.67	0.66	0.65	0.53
CRC stage III identified ***	0.58	0.55	0.56	0.58	0.58	0.54	0.53	0.52	0.51	0.39
CRC stage IV non-identified***	0.21	0.17	0.19	0.20	0.20	0.16	0.15	0.14	0.13	0.01
CRC stage IV identified***	0.21	0.17	0.19	0.20	0.20	0.16	0.15	0.14	0.13	0.01
Follow-up CRC I year 1-4**	0.74	0.70	0.71	0.73	0.62	0.69	0.68	0.67	0.66	0.54
Follow-up CRC II year 1-4**	0.74	0.70	0.71	0.73	0.62	0.69	0.68	0.67	0.66	0.54
Follow-up CRC III year 1-4**	0.65	0.62	0.63	0.65	0.54	0.61	0.60	0.59	0.58	0.46
Follow-up CRC IV year 1-4**	0.21	0.17	0.19	0.20	0.09	0.16	0.15	0.14	0.13	0.01
Follow-up CRC I year 4+**	0.78	0.74	0.76	0.77	0.66	0.74	0.72	0.71	0.70	0.58
Follow-up CRC II year 4+**	0.71	0.68	0.69	0.71	0.60	0.67	0.66	0.65	0.64	0.52
Follow-up CRC III year 4+**	0.67	0.64	0.65	0.67	0.56	0.63	0.62	0.61	0.60	0.48
Follow-up CRC IV year 4+**	0.45	0.41	0.43	0.44	0.34	0.41	0.39	0.38	0.37	0.25
Waiting state after neg. colonoscopy**	0.86	0.83	0.84	0.86	0.75	0.82	0.81	0.80	0.79	0.67

**(Scientific Institute of Public Health., 2013)*

*** Assumption;*

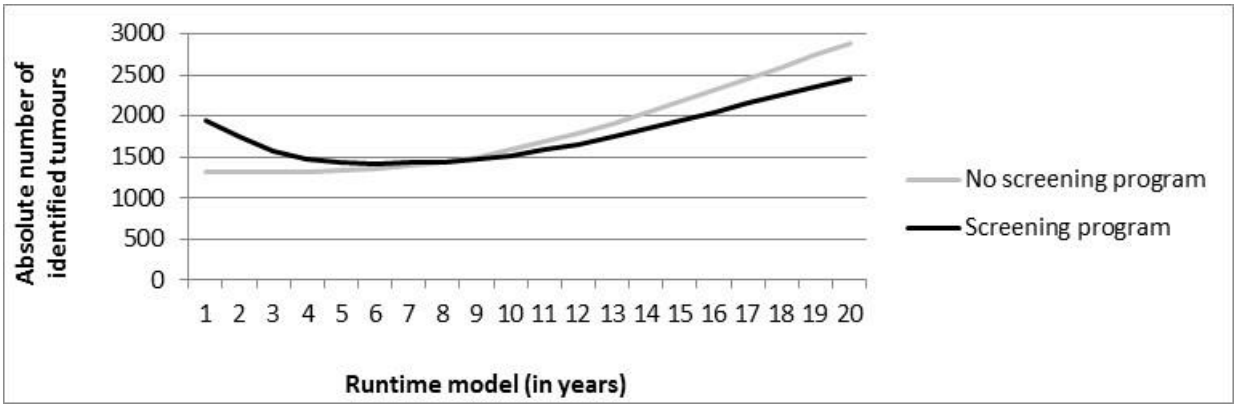
****(Cronin et al., 2013; Ness, Holmes, Klein, & Dittus, 1999)*

Appendix Table 6: Unit costs in €, 2014 prices

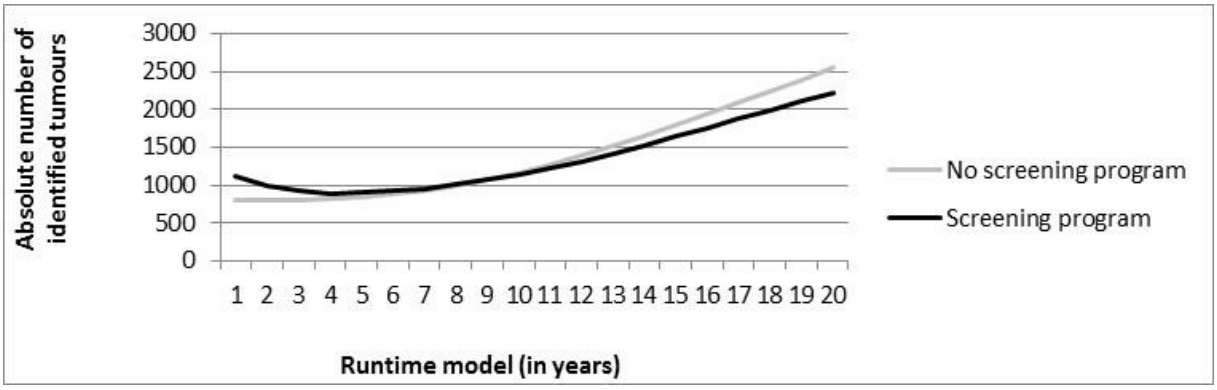
Model parameter	Input value		
	Health care payer	***Patient***	***Total***
Medical cost diagnosis[1]			
Non-adenomatous polyps and low-risk adenoma	€ 375	€ 18	€ 393
High-risk adenoma	€ 375	€ 18	€ 393
CRC I	€ 424	€ 33	€ 457
CRC II	€ 424	€ 33	€ 457
CRC III	€ 556	€ 36	€ 592
CRC IV	€ 556	€ 36	€ 592
Medical cost treatment, first year[2]			
CRC I	€ 11,399	€ 1,409	€ 12,808
CRC II	€ 20,217	€ 2,499	€ 22,716
CRC III	€ 27,902	€ 3,449	€ 31,351
CRC IV	€ 33,258	€ 4,111	€ 37,369
Medical cost follow-up (first 4 years after treatment)[2]			
CRC I	€ 7,756	€ 408	€ 8,165
CRC II	€ 5,859	€ 308	€ 6,167
CRC III	€ 3,972	€ 209	€ 4,181
CRC IV	€ 11,611	€ 611	€ 12,223
Medical cost follow-up, (4+)[2]			
CRC I	€ 180	€ 21	€ 202
CRC II	€ 180	€ 21	€ 202
CRC III	€ 3,972	€ 209	€ 4,181
CRC IV	€ 11,611	€ 611	€ 12,223
Cost of productivity loss			
Cost per day absenteeism[3]			€ 261
Number of days off work[4]			
CRC I		51	
CRC II		51	
CRC III		84	
CRC IV		148	
Death (based on friction cost method[5])		160	

1 Based on official Belgian nomenclature prices 2 (Pacolet et al., 2011) 3 (Cleemput et al., 2012) 4 (Hauglann, Saltyte, Fossa, Tveit, & Dahl, 2014) 5 (Hakkaart-van Roijen, 2010)

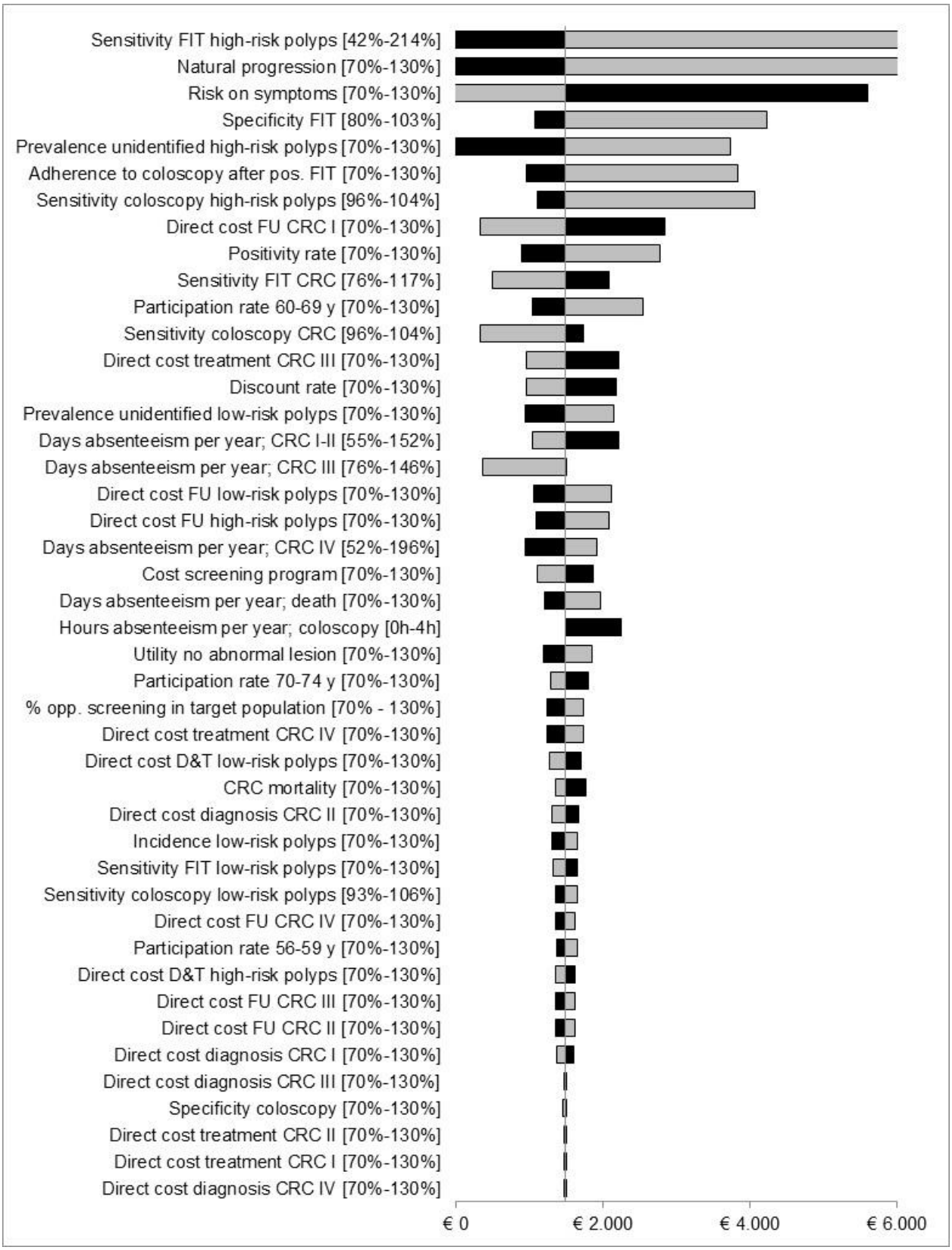
Appendix Figure 1a: Absolute number of identified tumours per year, in males aged 50+ (with inflow)



Appendix Figure 1b: Absolute number of identified tumours per year, in females aged 50+ (with inflow)



Appendix Figure 2a: Tornado-diagram showing the results of the one-way sensitivity analysis (males)

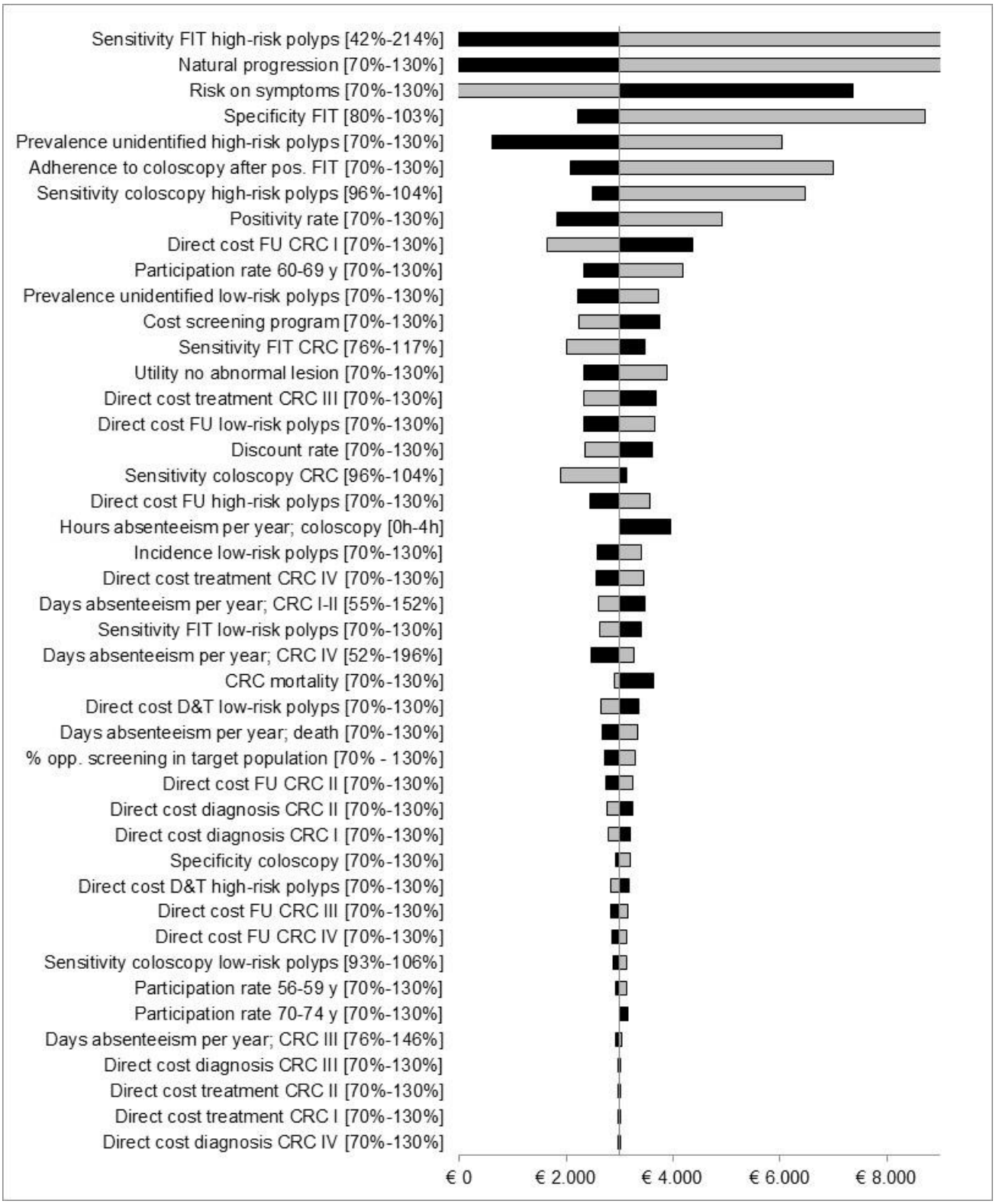


Range of variation in relative terms between brackets

D&T: diagnosis & treatment; FU: Follow-up

Dark-colored bars: maximum parameter value. Light-colored bars: minimu parameter value.

Appendix Figure 2b: Tornado-diagram showing the results of the one-way sensitivity analysis (females)



Range of variation in relative terms between brackets

D&T: diagnosis & treatment; FU: Follow-up

Dark-colored bars: maximum parameter value. Light-colored bars: minimu parameter value.

2.2.3. Cost-effectiveness and budget impact of population-based skin cancer screening

Lore Pil*; Isabelle Hoorens*, Katrien Vossaert, Vibeke Kruse, Isabelle Tromme, Niko Speybroeck, Lieven Annemans & Lieve Brochez. Cost-effectiveness of a population-based skin cancer screening. *JAMA Dermatology.* (*Accepted for publication).*

**Shared first authorship*

ABSTRACT

Importance: Several epidemiologic studies show an alarming global increase in the incidence of melanoma and non-melanoma skin cancer. Consequently the related health care costs are rising significantly.

Objective: To examine the cost-effectiveness of two population-based screening methods, namely a one-time total body examination and a one-time lesion-directed screening, as well as their budget impact and the impact on skin cancer epidemiology.

Design: A Markov model with a time horizon of 20 years analysed the cost-effectiveness (societal perspective) and budget impact (public health care payer perspective) of two population-based screening programs in Belgium, compared to the situation in the absence of a screening program (considering a threshold of 35,000/QALY gained)

Participants: In the health economic model, the total Belgian population aged 18+ was assumed to be invited for the screening program.

Main outcomes and measures: The impact of the screening program on skin cancer epidemiology and the cost per quality-adjusted life-year (QALY) gained of the two screening programs, compared to no screening program were evaluated, as well as the budget impact, expressed as the net costs for the health care payer over 50 years.

Results: Both screening strategies produced a gain in QALYs, resulting in incremental cost-effectiveness ratios of €31,360/QALY (€23,251/QALY – €41,468/QALY) in males and €18,051/QALY (€13,493/QALY – €23,019/QALY) in females for TBE and €34,170/QALY (€25,586/QALY – €44,831/QALY) in males and €18,999/QALY (€13,725/QALY – 25,139/QALY) in females for LDS. Additionally, a 4% decrease was predicted in the incidence rates of stage III&IV MSC at population level, in reference to the comparator. Skin cancer mortality was expected to decrease slightly due to the screening program with 5.6% in case of TBE and 1.0% in case of LDS, compared to no screening program. The budget impact analysis demonstrated that over a period of 20 years a one-time screening would induce an extra cost for the health care payer of €36 million in case of TBE or €6 million in case of LDS, respectively €4.1 or €0.7 per adult.

Conclusion and relevance: These results can be interpreted as cost-effective at a willingness-to-pay threshold of €35,000/QALY gained. Based on these results a TBE in general adult population (especially in the females; in males the results were less explicit) is the most cost-effective screening strategy and is predicted to result in a reduction of mortality over 20 years.

INTRODUCTION

The global skin cancer incidence is currently assessed to be between 2 and 3 million non-melanoma skin cancers and 132,000 melanoma skin cancers each year. It is estimated that one in every three cancers diagnosed is a skin cancer (WHO, 2016d). Despite the health burden, and despite the idea that early detection can lead to better cure rates and reduce the costs of disease, few studies have assessed the effectiveness and cost-effectiveness of screening strategies (Gordon & Rowell, 2015). Screening is a prevention strategy by which early detection changes the prognosis by a shift in stage distribution to earlier stages. However, these few currently available studies mainly addressed melanoma skin cancer (MSC) (Beddingfield, 2002; Freedberg, Geller, Miller, Lew, & Koh, 1999; Girgis, Clarke, Burton, & Sanson-Fisher, 1996; Gordon & Rowell, 2015; Losina et al., 2007), while non-melanoma skin cancer (NMSC) is also responsible for a large part of the direct medical health care costs of skin cancer (Stang et al., 2008), At this point, no evidence exists that population-based screening by means of a whole body examination is cost-effective (Bigby, 2010). In this study we compared the cost-effectiveness of two population-based screening strategies organised as a pilot study in Belgium, namely a one-time standard total body examination (TBE) versus a one-time lesion-directed approach (LDS) (Hoorens et al., 2016). The LDS approach, in which participants are seen with only a specific lesion of concern meeting certain pre-set criteria, was shown to result in lower participation rates but similar skin cancer detection rates as in TBE. In reference to TBE, LDS was time-saving for the physician. Details on the results of these two screening methods are described elsewhere (Hoorens et al., 2016). In addition to the cost-effectiveness analysis, a budget impact analysis of both screening strategies was performed to evaluate the impact on the public health care budget.

METHODS

Screening strategies

The modelled screening strategies were based on a skin cancer screening trial which has been organised in Belgium in 2014, comparing TBE to LDS in two socio-demographically comparable regions (Hoorens et al., 2016). The TBE was organised in a community of 9325 inhabitants (Wichelen, East-Flanders, Belgium) during a 5-day screening (March 14-18, 2014). All inhabitants 18 years and older received a personal invitation. The LDS was organised in a comparable community in terms of genetic background, socioeconomic status, culture, and geographic area (Nevele, East-Flanders, Belgium) (April 22 and 25-27, 2014), of which the inhabitants (9,484) were invited for a free-of-charge skin cancer check for a specific lesion meeting or more of the following listed criteria: ABCD rule (A, asymmetry; B, borders; C, colours; and D, differential structures), ugly duckling sign, new lesion lasting longer than 4 weeks, or red non-healing lesions. All participants (1668 TBE and 248 LDS) were screened by a team of six dermatologists using both naked-eye inspection and dermoscopy. In case of a suspicious lesion, the patient received a referral letter for his or her general practitioner or a dermatologist. As expected, the participation rate was higher in the TBE region compared to the LDS region (17.9% versus 3.3%, P

= < 0.01). Skin cancer yield did not differ significantly between both groups (2.3% TBE versus 3.2% LDS, P = 0.40). Further details on the design of this trial can be found in Hoorens et al. (2016).

Model structure

The Markov model was developed in Microsoft Excel® 2013, complemented with Visual Basic, and incorporated MSC as well as BCC and SCC. It consisted of different disease states: undiagnosed skin cancer, diagnosis & treatment, follow-up and death, separated per skin cancer stage. The same model design has been used before to estimate the cost-effectiveness of a skin cancer sensitisation campaign and a total ban on sunbed use. More information on the design of the model can be found in (Pil et al., 2016a) (Chapter 2.1.3. in this PhD thesis). All Belgian adult males and females were assumed to be invited for the single screening program. Modelled clinical outcomes of the screening were pathologically confirmed skin cancer, a false positive result or a (false) negative result. It was assumed that persons with an undiagnosed lesion who chose not to participate in the screening program or persons with a false negative result could have their lesion diagnosed by spontaneous clinical detection in the same cycle. Spontaneous clinical detection was also possible in the comparator (i.e. current situation). The duration of the diagnosis & treatment phase was 6 months (= 1 cycle) for patients with BCC, SCC 0-II or MSC I-II and 1 year for patients with SSC III-IV or MSC III-IV. To assign a higher probability of skin cancer death in the first years after diagnosis in case of SCC IV and MSC IV, the follow-up phase was divided into intense- and long-term follow-up, which lasted for 4 years, after which one moved into long-term follow-up. Patients in follow-up remained in this state until the end of the model's time horizon, or until they died. MSC and SCC stages were determined according to the 7th edition of the Tumour-Nodes-Metastases-classification for malignant tumours (Sobin et al., 2009). Stages for BCC were defined as <1cm, 1-2cm, >2cm and aggressive histology. BCC and SCC patients were assigned higher risk to develop an MSC lesion. Risk of a recurrent lesion was included in the model, risk of subsequent similar lesion (for all cancer types) was accounted for in the costs, since the effect of a subsequent lesion on the quality of life has not yet been described in current literature. All cohort members started the model in one of the model states, according to the baseline prevalence of BCC, SCC and MSC (Belgian Cancer Registry, 2013; Integraal Kankercentrum Nederland, 2011). The Markov model served two aims, namely to evaluate the incremental cost-effectiveness ratio (ICER) (calculated as the net costs divided by the net health effects) from a societal perspective and considering a willingness-to-pay threshold of 35,000/QALY gained, as well as the budget impact, over a period of 20 years. The budget impact analysis estimated the net cumulative cost of the screening program (and consequent examinations, treatment and follow-up) for the public health care payer over a period of 20 years, while allowing new entrance of 18-year olds each cycle in the lesion-free state, who were subjected to the natural progression of skin cancer.

Model inputs

<u>Screening-related input parameters</u>

Screening-related input parameters are depicted in Table 1. We did not derive the test-characteristics of the dermoscopy from the screening trial, as only expert dermatologists were involved, which can bias

the test-characteristics. Therefore, the study of Chevolet et al. (2015) was used, in which the test-characteristics of the dermoscopy used by well-trained and less-trained dermatologists were calculated. Averages of these values were used in our model.

Epidemiological and clinical data

The epidemiologic and clinical data used for the model have been described in our previous study (Pil et al., 2016b) (see Appendix p.84-89 in this PhD-thesis).

Costs and health effects

Costs included the cost of screening, direct medical costs and costs due to productivity loss, expressed separately for the health care payer and for the patient. The total cost of the screening per screenee was calculated at €4.9 in the TBE group and €1.8 in the LDS group. This included the costs for the invitation, poster and flyers, the cost for renting a public place for screening, the cost for using medical equipment and the cost of total time spent by the dermatologists. The difference in cost was mainly due to the difference in duration of the two screening methods (TBE 5 times longer than LDS). Direct costs for treatment and follow-up and indirect costs due to productivity loss -because of screening participation (derived from the screening study), morbidity or early mortality- were calculated based on a medical consumption questionnaire returned by 287 Belgian skin cancer patients, multiplied by official Belgian unit costs (Cleemput et al., 2012; Rijksinsituut voor Ziekte- en Invaliditeitsverzekering (RIZIV), 2016).
Health effects of the screening were represented as the impact on quality-adjusted life-years (QALYs), which include the impact on the quality of life as well as the life-expectancy as a result of the stage shift. Direct and indirect costs as well as EQ-5D utilities are described in our previous skin cancer study (Pil et al., 2016b) (see Table 3 on p.75 in this thesis). Following the Belgian guidelines, health effects were discounted at 1.5% and costs at 3% (Cleemput et al., 2012).

Scenario- and sensitivity analysis

Several scenarios were tested: screening from the age of 40 years instead of 18 -since skin cancer tumours usually do not arise frequently in younger persons-, public health care payer perspective (exluding the costs due to productivity loss and the costs for the patient), extending the time horizon to 50 years instead of 20 years and screening every five or two years during a period of 20 years instead of only once (and assuming a time horizon of 50 years and with constant screening uptake rates, not linked to disease incidence or progression). Sensitivity of the results to changes in individual parameters was assessed by means of a deterministic one-way sensitivity analysis and a probabilistic sensitivity analysis. In order to test the parameters' influence on the result, parameters were varied guided by the confidence interval (CI), or varied by ±30% of their original value in case a CI was not available. A probabilistic sensitivity analysis created a credibility interval around the cost-effectiveness ratio by running 5,000 Monte Carlo simulations according to the distribution of the input parameters. Utilities and probabilities were varied according to a beta-distribution and costs according to a gamma-distribution.

Table 1: Screening-related input parameters

Parameter	Input value						
	18-29y	***30-39y***	***40-49y***	***50-59y***	***60-69y***	***70-79y***	***79+y***
Participation rate[1]							
TBE males	8.80%	13.60%	14.20%	20.50%	24.10%	18.30%	5.40%
TBE females	14.50%	20.10%	20.30%	24.00%	27.10%	18.60%	4.60%
LDS males	1.50%	2.10%	2.20%	3.80%	5.90%	3.70%	2.60%
LDS females	1.80%	3.30%	3.70%	2.70%	5.50%	2.70%	0.90%
Test characteristics[2]							
sensitivity dermoscopy BCC				83%			
SCC				83%			
MSC				74%			
specificity dermoscopy BCC				87%			
SCC				87%			
MSC				89%			

1 (Hoorens et al., 2016) 2 (Chevolet et al., 2015)

RESULTS

Impact on skin cancer epidemiology

Over a period of 20 years, the model estimated the one-time screening to result in a 4% decrease in the incidence rates of MSC stage III & IV at population level, in reference to the comparator. Moreover, both screening programs were estimated to have a positive, although modest, impact on mortality from skin cancer, with an absolute reduction of 628 deaths in case of TBE (273 in males and 355 in females) and 118 in case of LDS (57 in males and 61 in females). This corresponds to a relative mortality reduction of about 5.6% in case of TBE and 1% in case of LDS, in reference to the comparator.

Cost-effectiveness

Base case

Both screening strategies resulted in a gain in QALYs over a period of 20 years (Table 2). Incremental health effects and costs were in good balance, leading to incremental cost-effectiveness ratios of €33,072/QALY in males and €18,687/QALY in females for TBE and €34,836/QALY in males and €19,470/QALY in females for LDS, which can be interpreted as a moderate cost-effective result assuming a willingness-to-pay threshold in Belgium of €35,000/QALY gained (Nationale Bank van België, 2015; WHO, 2005b).

Table 2: Results of the cost-effectiveness analysis, over a period of 20 years, per 1,000 persons

	Incremental QALYs		Incremental Costs		ICER	
	males	*females*	*males*	*females*	*males*	*females*
TBE	0.20	0.34	€ 6,465	€ 6,383	€ 33,072	€ 18,687
LDS	0.04	0.05	€ 1,391	€ 977	€ 34,836	€ 19,470

TBE: total body examination; LDS: lesion-directed screening

QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio

Table 3: Results of the scenario analysis

	TBE (€/QALY gained)		LDS (€QALY gained)	
	males	*females*	*males*	*females*
ICER base case	33,072	18,687	34,836	19,470
Screening from 40 years	35,622	21,841	36,348	23,485
Public health care payer perspective	20,016	12,300	20,784	12,887
Time horizon 50 years	9,253	5,722	10,262	5,549
Screening every 5 years*	11,811	6,060	12,758	5,671
Screening every 2 years*	12,180	6,021	12,404	5,436
ICER probabilistic	31,360	18,051	34,170	18,999
(95% CI)	(23,251-41,468)	(13,493-23,019)	(25,586-44,831)	(13,725-25,139)

TBE: total body examination; LDS: lesion-directed screening

QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; prod. loss: productivity loss

** during 20 years, but with a time-horizon of 50 years*

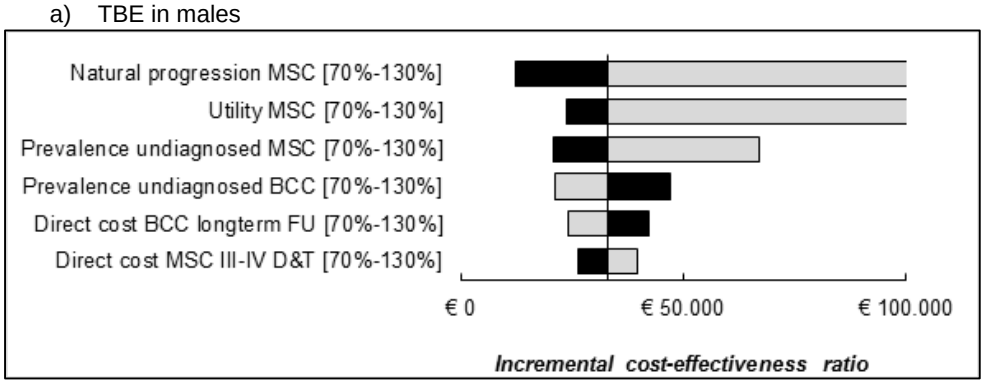
Scenario- and sensitivity analysis

Results from the scenario-analysis are presented in Table 3. A one-time screening from the age of 18 remained the most cost-effective strategy. From a public health care payer perspective, omitting the costs for the patient and the costs due to productivity loss, the result was better than from a societal perspective. Screening every two or five years had a lower cost-effectiveness ratio, but since the time horizon was set at 50 years for this scenario -as 20-year time horizon would not capture the effect of screening in e.g. year 18- it should be compared to the scenario of a one-time screening with a time horizon of 50 years. The one-way sensitivity analysis showed the most influencing parameters in the analysis for males to be the natural progression of MSC, the utility related to MSC, the prevalence of undiagnosed MSC and BCC, the direct cost BCC long term follow-up and the direct cost of MSC III and IV (Figure 1, tornado diagram shown for TBE). A higher value on these parameters led to a more cost-effective result, except for the prevalence of undiagnosed BCC and the direct cost of BCC follow-up, in which the effect was the opposite. Variation in these parameters resulted in ICERs exceeding the €35,000/QALY gained threshold in males; in females only the variation in the natural progression of MSC led to an ICER exceeding the threshold. The probabilistic sensitivity analysis created credibility intervals around the deterministic result. The cost-effectiveness planes, which are depicted in Figure 2, show that most simulations are located in the north-east quadrant and are below the willingness-to-pay

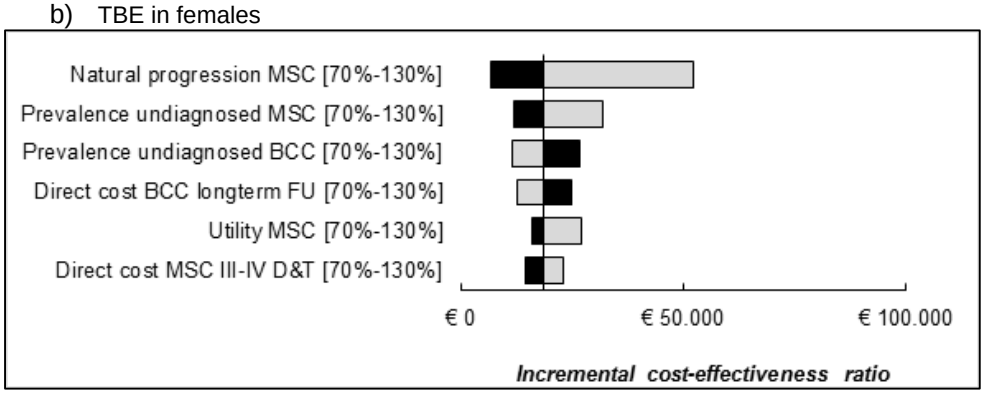
threshold of €35,000/QALY gained, although for the simulation in males part of the values are situated above the threshold. The cost-effectiveness acceptability curves (Figure 3) show that regarding a willingness-to-pay threshold of €35,000/QALY gained, the probability of screening being cost-effective is 79.7% and 59.9% for TBE and LDS in males and 100% in females.

Figure 1: Tornado diagrams with results of the one-way sensitivity analysis (for TBE)

a) TBE in males



b) TBE in females

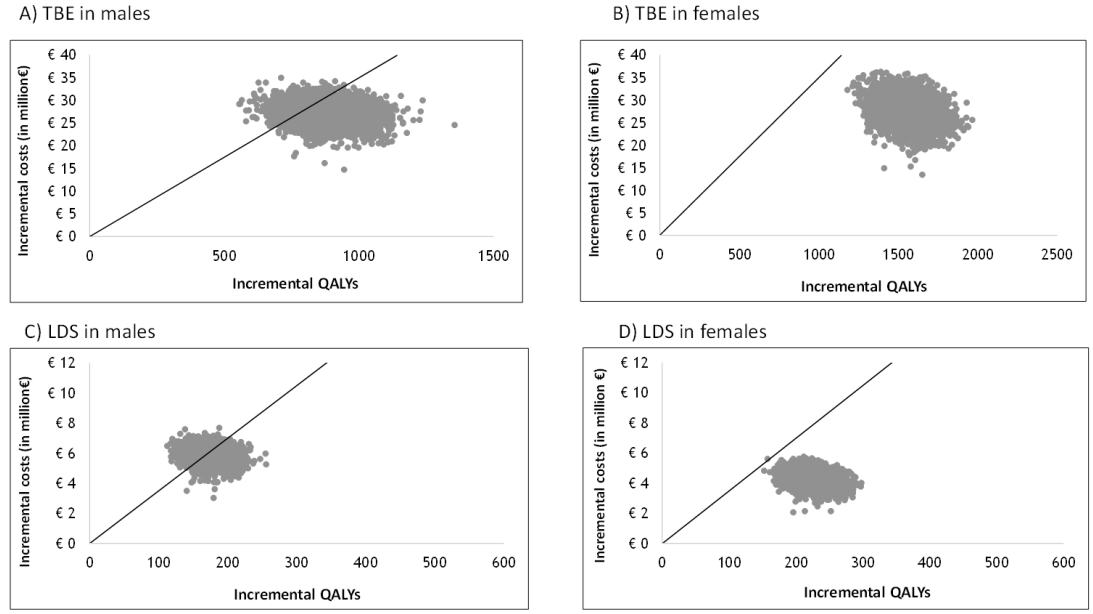


MSC: melanoma skin cancer; BCC: basal cell carcinoma: SCC: squamous cell carcinoma

D&T: Diagnosis and treatment; FU: follow-up

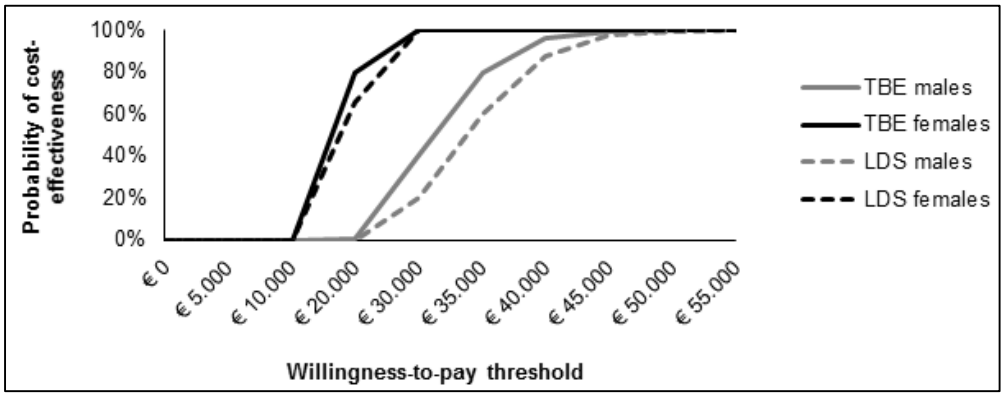
Light grey bars: minimum value of parameter; Dark grey bars: maximum value of parameter

Figure 2: Cost-effectiveness planes displaying the 5,000 simulations



Willingness-to-pay threshold of €35,000/QALY is displayed in the graphs

Figure 3: Cost-effectiveness acceptability curves



Budget impact

The budget impact analysis presented in Table 4, showed that over a period of 20 years a one-time screening would induce an extra cost for the health care payer of €36 million in case of TBE or €6 million in case of LDS, respectively €0.2 and €0.03 per year per person in the target group (18+).

Table 4: Results of the budget impact analysis, over a period of 20 years

	Cost of intervention	Health care payer	Total cost	Total net cost
Control	€ 0	€ 1,909,776,064	€ 1,909,776,064	
TBE	€ 7,308,319	€ 1,938,193,177	€ 1,945,501,496	€ 35,725,432
LDS	€ 463,275	€ 1,915,431,360	€ 1,915,894,635	€ 6,118,570

TBE: total body examination; LDS: lesion-directed screening

Model validation

The results of the skin cancer screening analysis resulted in detection rates similar the ones observed in the screening trial (Hoorens et al., 2016) (Appendix Table 1). Besides, the distribution of the cancer prevalence according to the tumour types over 20 years in the absence of the screening program was 69.9% BCC, 18.5% SCC and 11.6% MSC, which is in line with the observed 70% - 20% - 10% distribution (Integraal Kankercentrum Nederland, 2012b).

DISCUSSION

Over a period of 20 years, this analysis showed that a one-time TBE was estimated to lead to a gain of 2,380 healthy life-years in the total population (8.8 million) and a one-time LDS to 397 healthy life-years. In addition, TBE was projected to reduce skin cancer mortality by 5% over 20 years. However, currently no prospective studies support a reduction in skin cancer mortality due to screening. According to Boniol et al., the transient decrease in mortality in Schleswig-Holstein followed by return to pre-screening levels could reflect a temporal modification in the reporting of death causes (Boniol, Autier, & Gandini, 2015; Katalinic et al., 2012). In addition, no decrease in MSC mortality has been documented since the nation-wide skin cancer screening was introduced in Germany in 2013 (Katalinic, Eisemann, & Waldmann, 2015). Due to the screening cost, and the extra costs for treatment and follow-up, implementing a one-time screening costs extra money for the health care payer. Nevertheless, the balance between incremental costs and health effects is shown to be beneficial, both for TBE and LDS (ratio below the accepted threshold of €35,000/QALY gained), although in the case of males both screening strategies tend to this threshold limit. However, the probability of the screening's cost-effectiveness result being below the considered threshold was 80% in TBE and 60% in LDS. The incremental cost-effectiveness ratio for TBE was better than for LDS, which can be explained by the low participation rate in the LDS screening arm (Hoorens et al., 2016). Since the skin cancer detection rates were comparable in both screening arms and since LDS screening was time-saving, it could be worthwhile to investigate how participation in this type of screening could be increased. If the same participation rates of TBE would be attained in LDS, then LDS would be more cost-effective than TBE. Screening in females was clearly more cost-effective than in males, because of the higher prevalence and incidence of skin cancer in females in Belgium. Screening from the age of 40 instead of 18 only slightly deteriorated the cost-effectiveness result, probably because younger persons have a higher quality of life, which means that screening could gain more health benefits in younger persons, and because older persons have a higher risk to die from other causes than skin cancer, which disadvantages the beneficial effect of screening. Suppose the time horizon of the model would be extended to 50 years, then the cost-effectiveness ratio would be better than with a 20-year time horizon, as the benefit of the screening probably continues for a longer period than 20 years. The choice to implement the screening program repeatedly would be cost-effective, but a one-time screening would still be the most cost-effective strategy. When assuming a public health care payer perspective, omitting the extra costs for the patient and the costs due to productivity loss, screening becomes more cost-effective as those extra costs for the patient are not taken into account, lowering the total incremental cost. Sensitivity analysis showed that the natural

progression of skin cancer had the highest influence on the cost-effectiveness outcome, arguing for further research on the natural progression of skin cancer. Another important influencing parameter was the cost of MSC III and IV (for diagnosis and treatment). It is possible that the cost for treating MSC III and IV will keep on rising due to new (combinations of) drugs and other technologies, which would result in screening becoming more cost-effective. Also the prevalence of undiagnosed BCC and MSC was highly influential: a higher prevalence of undiagnosed MSC would lead to higher health benefits compensating for the extra costs, which would make the screening more cost-effective. However, in case of a higher prevalence of undiagnosed BCC, screening would become less cost-effective, as detecting and treating BCC does not lead to benefits in quality of life and lead to extra costs. Although treating small BCC lesions is less expensive than treating more advanced BCC lesions, it seems from this study that the extra costs for treating the BCC lesions would become too high. Furthermore, since a better sensitivity of dermoscopy leads to a better cost-effectiveness result (10th most influencing parameter), training initiatives for dermoscopy are recommended.

Other studies on the cost-effectiveness of skin cancer screening have been conducted especially in the U.S. and Australia and only included MSC. Most of these studies expressed the cost-effectiveness of MSC screening to no screening in cost per life-year saved. These studies showed that screening men over 50 years biennially by general practitioners resulted in a ratio of $12.137/life-year saved (AUD) (Girgis et al., 1996). A one-time screening by dermatologists in a self-selected population resulted in $51,481/life-year saved (USD) (Beddingfield, 2002) and in a high-risk population in $39.600/life-year saved (USD) (Freedberg et al., 1999). One study calculated the cost per QALY gained of a visual one-time screening from the age of 50 to be $10,100/QALY gained (USD) (~ €9,256/QALY gained) (Losina et al., 2007). When implemented biennially the ICER rose to $80,700/QALY (~ €73,882/QALY) and if annually to $586,800/QALY (~ €537,220/QALY). Our results supports this latter result of better cost-effectiveness in case of one-time screening. However, it is difficult to compare studies directly because of different screening setting (visual screening versus dermoscopy screening, composition of the screening team), different epidemiological backgrounds (cf. incidence of MSC higher in Australia than in Belgium) and different model design.

This is the first time that the costs and benefits of a skin cancer screening program have been analysed in detail. Not only the benefits of screening were captured in the model, but the impact of a false-positive screening result on quality of life in terms of psychological harms was included as well. However, in our model, the screening examination itself did not have an impact on the quality-of-life. The study of Collins et al. (2011) showed that screening (in general) does not appear to have an adverse emotional impact in the longer term and they stated that up to now too few studies have assessed the short term emotional impact of screening. The study of Hoorens et al.(2016) questioned the anxiety of the screenees right after the screening, but baseline levels were not available so no conclusions on the quality-of-life right before and after the screening could be deducted from this study. Beside the strengths of our analysis, some limitations should also be addressed. Firstly, in Belgium there is no accurate registration of NMSC. Therefore, we relied on epidemiologic results of the Dutch cancer registry, since they have a more systematic registration of NMSC. Secondly, accurate information on the natural progression of skin cancer is not available. Therefore, in our model, the natural progression was estimated based on

calibration. This is generally a more reliable approach than making assumptions on parameters based on limited studies. Lastly, it may be noted that screening parameters such as participation rate, test characteristics, as well as unit costs of detection, treatment and follow-up and epidemiologic parameters are context-specific limiting the direct transferability of the results across different countries. However, we believe that not only the mean result, but also the results from the sensitivity and scenario-analysis can be informing for other countries.

CONCLUSION

Based on this study, skin cancer screening was shown to be moderately cost-effective at a willingness-to-pay threshold of €35.000/QALY gained, especially in females. Based on these results a total-body examination in the general adult population (with particular focus on females) is the most cost-effective screening strategy from a societal viewpoint and projected to result in a mortality reduction over 20 years. The study indicates an important opportunity to collect observational data in support of the mortality reduction.

APPENDIX

Appendix Table 1: Model validation: observed versus calculated cancer detection rates from the screening

	Observed		Calculated	
	males	**females**	**males**	**females**
SCC 0-II	0.060%	0.060%	0.067%	0.061%
SCC III	0.007%	0.007%	0.007%	0.007%
SCC IV	0.002%	0.002%	0.003%	0.002%
MSC I	0.480%	0.480%	0.482%	0.478%
MSC II	0.102%	0.080%	0.103%	0.075%

Observed: parameter values observed in the screening trial

Calculated: estimated parameter values based on the model

Part 2: Original research studies: health economic evaluations in the continuum of prevention

2.3. Indicated prevention interventions

2.3.1. Cost-effectiveness of a helpline for suicide prevention

Based on:

Lore Pil, Kirsten Pauwels, Ekke Muijzers, Gwendolyn Portzky & Lieven Annemans. Cost-effectiveness of a helpline for suicide prevention. (2013). Journal of Telemedicine and Telecare 19 (5). p.273-281

ABSTRACT

Background: The cost-effectiveness and budget impact of a suicide helpline in Belgium was evaluated, consisting of a telephone- and a chat service.

Methods: An age- and gender-dependent Markov model with a ten-year time horizon and a one-year cycle length was developed, assuming a societal perspective, to predict cumulative costs and quality-adjusted life-years (QALYs) in the helpline users. The model included six transition states: the initial state (at risk), first attempt, re-attempt, follow-up, suicide and death from other causes. Data on the effect of the helpline and costs associated with model states were obtained from the literature. One-way and probabilistic sensitivity analyses were performed to capture uncertainty. In addition, the budget impact of the helpline was analysed.

Results: Over ten years, the telephone- as well as the chat service could avoid about 36% of suicides and attempts in this high-risk population. In males, 0.063 QALYs (95% confidence interval, CI 0.030-0.097) and 0.035 QALYs (95%CI -0.026-0.096) were gained by users of the telephone- and chat service respectively. The corresponding values for females were 0.019 QALYs (95%CI -0.015-0.052) and a QALY-neutral result of -0.005 (95%CI -0.071 -0.062). There were net societal savings of respectively €2,382 (95%CI 1,953-2,859) and €2,282 (95%CI 1,855-2,758) per person in male users; €2,171 (95%CI 1,735-2,664) and €2,458 (95%CI 1,945-3,025) in female users. At the population level, €1,452,022 could be saved for the public health service (national health insurance), mainly due to the telephone service.

Conclusion: The analysis predicted that both means of telemedicine for suicide prevention in Flanders are cost-saving, and have a modest effect on QALYs.

INTRODUCTION

Suicide is an important public health problem in Flanders (Belgium). The annual suicide rate is nearly twice as high as the European average (Vlaams Agentschap Zorg en Gezondheid, 2012b; WHO, 2012c). Every day more than three people commit suicide and 26 people attempt suicide in Flanders (De Jaegere, Wittouck, Portzky, & Van Heeringen, 2009). There is an urgent need to reduce the incidence of suicidal thoughts, utilising evidence-based prevention interventions and policy action (Jacka & Reavley, 2014). A suicide helpline is one type of such prevention interventions, targeting high-risk individuals with (minimal) signs of suicidal thoughts and plans and aiming to reduce the suicidal state of the helpline user. The conventional telecommunication medium for suicide prevention is a telephone service, but new communication channels like the Internet can also be used (Krysinska & De Leo, 2007; Luxton, June, & Kinn, 2011). In Flanders, the suicide helpline De Zelfmoordlijn has provided a crisis service since 1979, first by telephone, and since 2005 by online chat sessions as well. Unlike chat rooms, the chat service of De Zelfmoordlijn allows people to have an individual conversation with a trusted person. In 2011, 3785 people contacted the helpline seeking personal help. In this study, a cost-effectiveness analysis and budget impact analysis of the Flemish suicide helpline was conducted.

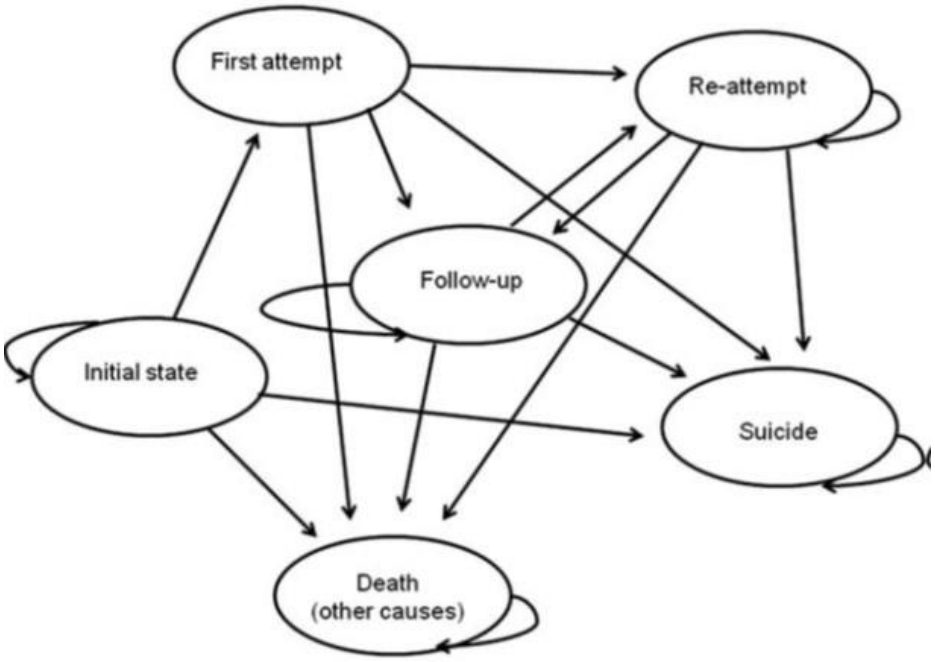
METHODS

Model structure

The analysis was based on an age- and gender-dependent state transition Markov model, predicting life events for users of the suicide helpline in 2011. The target population consisted of 3785 unique users of the suicide helpline, who call/chat for themselves, of which 2418 women (64%) and 1367 men (36%). In women there were 1840 telephone- and 578 chat service users, in men 1201 telephone- and 166 chat service users. Mean age of the population was 37 years (range 12 to 91 years), with 21 years in the chat service group and 42 years in the telephone service group. Predictions were made from the contact with the helpline over a period of ten years for two scenarios: a scenario in which the suicide helpline was present and a scenario in which the suicide helpline was absent. Six states, which we considered the most important in the suicidal process of an individual, were included in the model: the initial state (i.e. at risk for suicide), first attempt, follow-up, re-attempt, suicide and death from other causes (Figure 1). Transitions between these states were allowed once a year. All individuals in the target population started the model in the initial state (i.e. people who seek for personal help and who had not made an attempt before), consisting of helpline users with no to mild suicidal thoughts as well as users with moderate to strong suicidal thoughts (i.e. those who are categorised in one of the three most severe states of the suicidal process). This categorisation was based on information registered by the Centre for Prevention of Suicide (Table 1) (2012). During the first year after the contact, individuals could move to another state - i.e. they could attempt suicide, commit suicide or die due to another cause- or remain in the initial state. From the second year onwards, transitions to more states were possible: making a re-attempt or moving to the follow-up state (i.e. state one moves to after an attempt). The attempt state was a transitional state, i.e.

individuals only remained in this state for one cycle, after which they moved to follow-up, re-attempt, suicide or death (from another cause). All individuals stayed in the model for ten years. At the start of the model, they were distributed among 14 age categories. Analyses were performed separately for males and females, and for both telephone- and chat services. The analysis assumed a societal perspective, using the friction cost method for assessing the cost due to productivity loss (Hakkaart-van Roijen, 2010; Koopmanschap & van Ineveld, 1992). The difference in costs over ten years was divided by the net effects in quality-adjusted life-years (QALYs), in order to obtain the primary outcome measure, the incremental cost-effectiveness ratio (ICER). Annual discount rates of 3% and 1.5% were applied to future costs and effects respectively, as recommended by the Belgian Knowledge Centre for Health care (Cleemput et al., 2012). In order to estimate the budget impact, net costs during one cross-sectional year were simulated by repeating the model outcomes in one cohort for subsequent annual cohorts.

Figure 1: Markov model of health states and possible transitions during each 1-year cycle.



The ellipses represent the possible states and the arrows correspond to transition probabilities

Table 1: proportion of suicidal thoughts in the helpline users at baseline and after an attempt (= follow-up)

	Telephone		Chat	
	males	**females**	**males**	**females**
No to mild suicidal thoughts[a]	53.6%	52.2%	44.9%	40.8%
Moderate to strong suicidal thoughts[a]	46.4%	47.8%	55.1%	59.2%
No to mild suicidal thoughts at follow-up[b]	81.2%	81.2%	81.2%	81.2%
Moderate to strong suicidal thoughts at follow-up[b]	18.8%	18.8%	18.8%	18.8%

a (Centrum ter Preventie van Zelfdoding, 2012); b (De Jaegere, Wittouck, Portzky, & Van Heeringen, 2010)

Follow-up: only three days after attempt (cf. De Jaegere et al., 2010). These prevalences at follow-up are only used to estimate the utility associated with the follow-up state.

Transition probabilities

The age- and gender-dependent transition probabilities between the model states were derived from published literature, official Flemish databases and data from the Flemish Centre of Suicide Prevention, the latter specific for the target population (Table 2). The annual risk of attempting suicide for the first time was calculated as a weighted average of the risk of helpline users with no to mild suicidal thoughts, (ranging from 0.012% to 0.36%; gender- and age-specific, based on suicide statistics of the Flemish population (Boffin et al., 2010; Vlaams Agentschap Zorg en Gezondheid, 2012b)) and helpline users with moderate to strong suicidal thoughts, (ranging from 5.6% to 8.5%; gender- and age-specific (May et al, 2012)) (Table 2). May and colleagues (2012) found in their ten-year follow-up study that two thirds of those individuals with suicidal thoughts who made an attempt, made that attempt in the first 2.5 years after baseline measurement and one third between year 2.5 and year 5. Based on this study, transition probabilities to the attempt state were varied according to the time one remains in the initial state. Probabilities of making an attempt from the study of May et al. (2012) were used for years 1-3 and years 4-5. After 5 years, the average Flemish population risk was assigned to the individuals who still remained in the initial state (Boffin, Bossuyt, & Van Casteren, 2010; De Jaegere et al., 2010). The annual risk to commit suicide was calculated in the same way (May, Klonsky, & Klein, 2012). These transition probabilities for making an attempt and committing suicide were age-adjusted according to the Flemish suicide statistics (Vlaams Agentschap Zorg en Gezondheid, 2012b). The annual risk of committing a non-fatal re-attempt within the first year after the first attempt was derived from the study of Tejedor et al. (1999) and amounted to 6.5% per year. In the subsequent eight years after the first attempt this risk decreased to 1.7% per year. The annual probability to complete a fatal re-attempt during the period of 10 years was 1.3% (Tejedor, Diaz, Castillon, & Pericay, 1999). These risks were made gender- and age-adjusted based on the age distribution of attempts and suicides in the Flemish population. The annual risk of dying from another cause was obtained by Flemish life tables (Vlaams Agentschap Zorg en Gezondheid, 2012a).

Table 2: Ranges of annual transition probabilities (in %), dependent on gender, age and telephone- or chat-service group (2010), and base-case annual costs per model disease state (2012 values).

	Females (%)	Males (%)
First attempt year 1-3[1]	2.70-5.19	1.86-4.65
First attempt year 4-5[1]	1.32-2.60	0.91-2.30
First attempt year 6-10[2]	0.03-0.36	0.01-0.25
Suicide year 1-3[1]	0.06-2.25	0.22-3.23
Suicide year 4-5[1]	0.03-1.10	0.11-1.58
Suicide year 6-10[1]	0.00-0.03	0.00-0.05
Non-fatal re-attempt year 1[3]	4.84-7.39	3.43-7.17
Non-fatal re-attempt year 2-10[3]	1.24-1.9	0.88-1.84
Fatal re-attempt[3]	0.11-3.28	0.4-5.05
Death (from other causes)	0.01-6.00	0.01-8.85
	Direct costs (€)	**Indirect costs (€)**
Initial state[4]	-	1,526
(Re-)Attempt[5]	2,933	43,434
Follow-up[6]	89	1,526
Suicide[7]	2,600	60,537

1 (Boffin et al., 2010; Centrum ter Preventie van Zelfdoding, 2011; De Jaegere et al., 2010; May et al., 2012; Vlaams Agentschap Zorg en Gezondheid, 2012b). 2 Flemish population risk (Boffin et al., 2010; De Jaegere et al., 2010; Vlaams Agentschap Zorg en Gezondheid, 2012b) 3 (Boffin et al., 2010; De Jaegere et al., 2010; Tejedor et al., 1999) 4 Average number of days absenteism + (Securex, 2010) 5 (Corso, Finkelstein, Miller, Fiebelkorn, & Zaloshnja, 2006; Securex, 2010; Verschraegen, 2007) 6 (Corso et al., 2006; Securex, 2010) 7 (Corso, Mercy, Simon, Finkelstein, & Miller, 2007; Securex, 2010)

Cost data

Direct and indirect costs associated per model state are shown in Table 2 (2012 values). The direct cost of a suicide attempt is the weighted sum of Belgian costs assigned to hospitalisation (92%) and general practitioner consultations (8%) (Corso et al., 2006; Verschraegen, 2007). Because of lack of data on the annual cost of suicide in Belgium or Europe, an estimation of the direct cost of suicide was derived from the American study of Corso et al. (2007) (converted to euro using the purchasing power parity and indexed to 2012). This cost includes ambulance transport, medical examiner costs, emergency department, inpatient hospitalisation and/or nursing home costs. The direct medical cost associated with the follow-up was based on the ratios for long term medical costs from the study of Corso et al. (2006), which were 30% and 14% of the costs due to an attempt, for admitted and non-admitted cases respectively. Costs due to productivity loss were calculated by multiplying the unit cost of one day of absenteeism (€280) (Securex, 2010) with the average annual days of absenteeism per working individual both in general (5.7) (Securex, 2010) as well as specifically due to a suicide attempt (assumed to be 162, weighted average of full-time and part-time working individuals (Algemene Directie Statistiek en Economische informatie, 2011; Draper, 1994) or suicide (assumed to be one year, weighted for of full-time and part-time working individuals). The friction cost method assumes

the costs to lost productivity due to suicide only to be applied in the year in which the suicide was committed (Hakkaart-van Roijen, 2010). Because not all individuals in the model were at productive age during the ten years, the indirect costs were not applied to age categories under 20 years and age categories from 60 years on (as the average age of retirement in 2011 was 62 years). The total cost of 'De Zelfmoordlijn' for 2011, including salaries, transport costs of personnel, compensation for the trained volunteers, operation costs and costs of telephony and instant messaging, equals €218,299. This cost was divided by the total number of people reached by the helpline (5054; including those who made use of the helpline for the benefit of others), and amounted to €43 per person. This cost was added once per individual, namely at the point where the individuals start in the model.

Quality of life data

The total cohort started the model in the initial state, which consists of helpline users with moderate to strong suicidal thoughts and users with no to mild suicidal thoughts. The utilities associated with the initial state were calculated as the weighted average of the utility related to suicidal thoughts and the utility in the general Belgian population. An average EQ-5D utility for suicidal thoughts (0.64, 95%CI: 0.33-0.95) and a suicide (re-)attempt (0.54, 95%CI: 0.29-0.79) were derived from the study of Van Spijker et al. (2011). In Belgium, utilities in the general population are currently only available as scores on a visual analogue scale (Szende & Williams, 2004). To convert these scores to EQ-5D index utilities, both were plotted per health state. A linear relation was assumed between them, so the best fitting regression line was used to calculate the EQ-5D index values. Utilities associated with the follow-up state were calculated as the weighted average of the utility related to the general Belgian population and to suicidal thoughts, based on the proportion of the target population with suicidal thoughts at follow-up (De Jaegere, Wittouck, Portzky, & Van Heeringen, 2010). The age-dependent base-case utilities are shown in Table 3.

Table 3: Age-dependent base-case utilities per state; initial state utilities separated according to gender

Age	Initial state telephone		Initial state chat		Attempt	Follow-up
	female	*male*	*female*	*male*	*female/male*	*female/male*
10-17	0.777	0.780	0.757	0.764	0.578	0.829
18-29	0.753	0.755	0.733	0.74	0.559	0.803
30-39	0.727	0.729	0.708	0.715	0.54	0.775
40-49	0.726	0.728	0.707	0.714	0.539	0.774
50-59	0.699	0.701	0.68	0.687	0.519	0.745
60-69	0.686	0.688	0.668	0.674	0.509	0.731
70-79	0.615	0.617	0.599	0.605	0.457	0.656
80+	0.611	0.613	0.595	0.601	0.454	0.652

Relative risk reduction: effect of the intervention

Studies supporting the effectiveness of telephone- and chat services in suicide prevention are scarce (Gould, Kalafat, Harrismunfakh, & Kleinman, 2007; Krysinska & De Leo, 2007; Scott & Guo, 2012). The main barriers for conducting randomised controlled follow-up studies in suicide prevention are the principles of anonymity and confidentiality. Currently no effectiveness study of the Flemish suicide helpline has been performed. Lester (1997) found some evidence for the effectiveness of suicide prevention centers in the U.S. Gould et al. (2007), conducted a pre- and post-test immediately before and after a call to a U.S. crisis hotline, to assess the proximal effect. Before the call, 43% of the users had a moderate to strong intent to die (3 or more on a 5-point scale). After the call, this proportion had decreased to 25%, which shows a relative risk reduction of 40.98%. The relative risk reduction calculated by Gould et al. was applied to our Flemish suicide helpline. This could be justified by two main arguments. First, both the suicide helpline in our study and the US suicide helplines work in a similar way (e.g. both are staffed by trained volunteers who keep call records) (Kalafat, Gould, Munfakh, & Kleinman, 2007). Second, the proportion of individuals in the study of Gould et al. with a moderate to strong intent to die (43%) approximates the number of people with moderate to strong suicidal thoughts in our model (47%) [265]. Assuming the suicide helpline can lower the amount of individuals with moderate to strong suicidal thoughts, suicidal acts can be prevented since the risk of making an attempt or committing suicide is based on the proportion of individuals with suicidal thoughts. Fukkink and Hermans (2009) investigated the effect of the telephone- and chat service of a child helpline in the Netherlands. They found a positive effect of the helpline, but there were no significant differences in effect sizes between the telephone- and chat service. Hence, in our model the same relative risk reduction was used for the chat- as for the telephone service, which means that both should have an equally strong impact on the amount of suicidal thoughts and thus on suicides and suicide attempts. The effect of the intervention was applied in the first five years after the call, after which no further effect was applied.

Sensitivity analyses

One-way and probabilistic sensitivity analyses were carried out to capture uncertainty in the key parameters. The effect of costs, utility of suicidal thoughts, utility of making an attempt, incidences of attempts and suicides in suicidal individuals, the relative risk reduction and the discount rate on net costs and net QALYs was evaluated in case of better or worse conditions of these parameters, defined by an increase or decrease of 30%. A probabilistic analysis varied costs, utilities and the relative risk reduction by their own probability distribution. Cost data were assumed to be distributed according to a gamma-distribution, utilities according to a beta-distribution and the relative risk reduction according to a log-normal distribution (Briggs et al., 2006). Several scenario analyses were conducted in order to assess the effect of different methodological choices. In the first scenario we evaluated the effect of a continuing risk over the 10 years to make a first attempt instead of a decreasing risk, assuming individuals to remain equally suicidal during the years they remain in the initial state. In a second scenario analysis the effect of decreasing the utilities of the follow-up state to the level of utilities of the initial state was investigated. In a third scenario the effect of using the human capital method instead of the friction cost method was

assessed, applying the cost due to productivity loss for a lifetime and in a final scenario the change in the ICER was explored when excluding the costs due to productivity loss.

RESULTS

Base-case analysis

It was estimated that over a period of 10 years about 36% of suicides and first suicide attempts would be avoided in the population of high-risk helpline users by means of the telephone service as well as by means of the chat service of the suicide helpline. This represents 205 attempts and 33 suicides. In relative terms, 16 suicides and 47 first suicide attempts would be prevented in 1,000 males with the telephone service and 10 suicides and 60 first suicide attempts with the chat sessions. In 1,000 females the telephone service would lead to the prevention of 6 suicides and 54 first suicide attempts, while 2 suicides and 68 first suicide attempts would be avoided by the chat sessions. In the situation where the helpline is available, female users of the telephone service would gain 0.019 QALYs, but in the chat service there was almost a neutral result (-0.007) (Table 4). The telephone service seems to lead to more health gains than the chat service, especially in male users. An increase of 0.064 and 0.046 QALYs respectively was found in males. Differences in costs between the chat- and telephone service were less clear. Total costs would decrease by €2,171 and €2,457 in female users of telephone- and chat service respectively, and by €2,366 and €2,272 respectively in males. Differences in costs between the chat- and telephone service are less clear. These outcomes for one cohort were repeated for subsequent annual cohorts in order to simulate the costs and effects during one cross-sectional year. It was estimated that over a period of 10 years, the suicide helpline in Flanders would save €1,452,022 for the public health service (national health insurance) (equaling €4 per year per contact person); €1,188,519 through the telephone service and €263,503 through the chat service.

Table 4: Results in the base case and sensitivity analyses, expressed in net QALYs and net costs over a period of 10 years

	Results in users of the telephone service				**Results in users of the chat service**			
	males		**females**		**males**		**females**	
	net QALYS	*net costs*	*net QALYS*	*net costs*	*net QALYS*	*net costs*	*net QALYS*	*net costs*
Base case deterministic*	0.064	€ -2,366	0.019	€ -2,171	0.046	€ -2,272	-0.007	€ -2,457
Continuing risk of attempt/suicide	0.070	€ -2,470	0.020	€ -2,266	0.053	€ -2,185	-0.010	€ -2,340
Utilities FU = initial state	0.077	€ -2,366	0.035	€ -2,171	0.069	€ -2,272	0.024	€ -2,457
Human capital method	0.064	€ -5,801	0.019	€ -3,105	0.046	€ -4,404	-0.007	€ -3,002
Excl. productivity loss	0.064	€ -165	0.019	€ -171	0.046	€ -204	-0.007	€ -219
Base case probabilistic	0.064	€ -1,222	0.019	€ -1,088	0.045	€ -1,192	-0.008	€ -1,237
95% CI	(0.057–0.084)	(€-2,498–€-1,995)	(0.013–0.038)	(€-2,307–€-1,790)	(0.036–0.074)	(€-2,401–€ -1,908)	(-0.018–0.023)	(€-2,608–€-2,050)

*Base case = decreasing risk on attempt in year 4-5 and from year 6-10, effect of helpline continuing for 5 years, utility related to follow-up calculated as the average of the utility of the general Belgian population and the utility associated with suicidal thoughts

FU: Follow-up

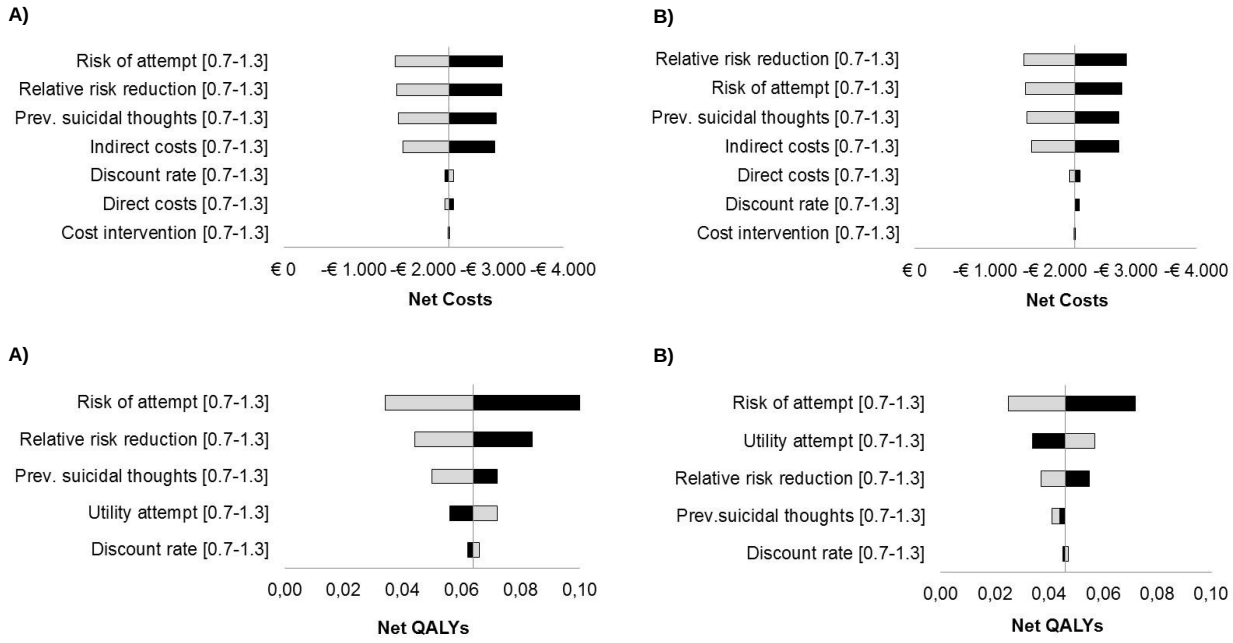
Sensitivity- and scenario analyses

One-way sensitivity analyses, for male and female users of the telephone- and chat service, assessed the effect of uncertainty in parameters on net QALYs and net costs (Figure 2, tornados shown for male users). The uncertainty in the risk of making an attempt, the utility associated to a suicide attempt, the relative risk reduction due to the helpline and the prevalence of suicidal thoughts had the highest influence on the QALY gain, although the impact was only minimal. A higher risk of making an attempt, a higher relative risk reduction and a higher prevalence of suicidal thoughts in the target population would result in a higher QALY gain, whereas a higher utility associated with an attempt would result in a lower QALY gain. The net cost result was mostly influenced by the risk of making an attempt, the relative risk reduction due to the helpline, the prevalence of suicidal thoughts and the indirect costs due to productivity loss. However, the impact was only minimal.

A scenario analysis with a continuing risk of making a first attempt or conducting suicide instead of a decreasing risk after being in the initial state for some years resulted in slightly higher QALY gains and cost-savings (Table 3). A second scenario took into account the fact that the utilities for the follow-up state are quite uncertain since the follow-up period was only 3-4 days after the attempt. As we assume that the degree of suicidal thoughts will increase with time since the attempt, a scenario was simulated in which the utilities of the initial state were applied tothe follow-up state. The results changed in a positive way: the base case gain in QALYs increased to 0.077 and 0.069 in males for telephone and chat service respectively, and to 0.035 and 0.024 in females for telephone and chat service respectively. Applying the human capital method instead of the friction cost method generated higher cost savings, especially in males. Omitting costs due to productivity loss would worsen the result, although there would still be cost-savings.

Second order Monte Carlo analyses were performed to assess the effect of the uncertainty associated with the risk of making an attempt, the relative risk reduction, utilities and costs simultaneously. The cost-effectiveness planes show that cost and QALY points are mainly situated in the south-east quadrant of the cost-effectiveness plane, except in the case of female users of the chat service (Figure 3). In the analysis for female users of the chat service, only 33% of the simulations showed a gain in QALYs, in contrast to the 99% probability of a QALY gain in male users of the chat service. Based on the probabilistic sensitivity analyses, credibility intervals (95%) were generated (Table 4).

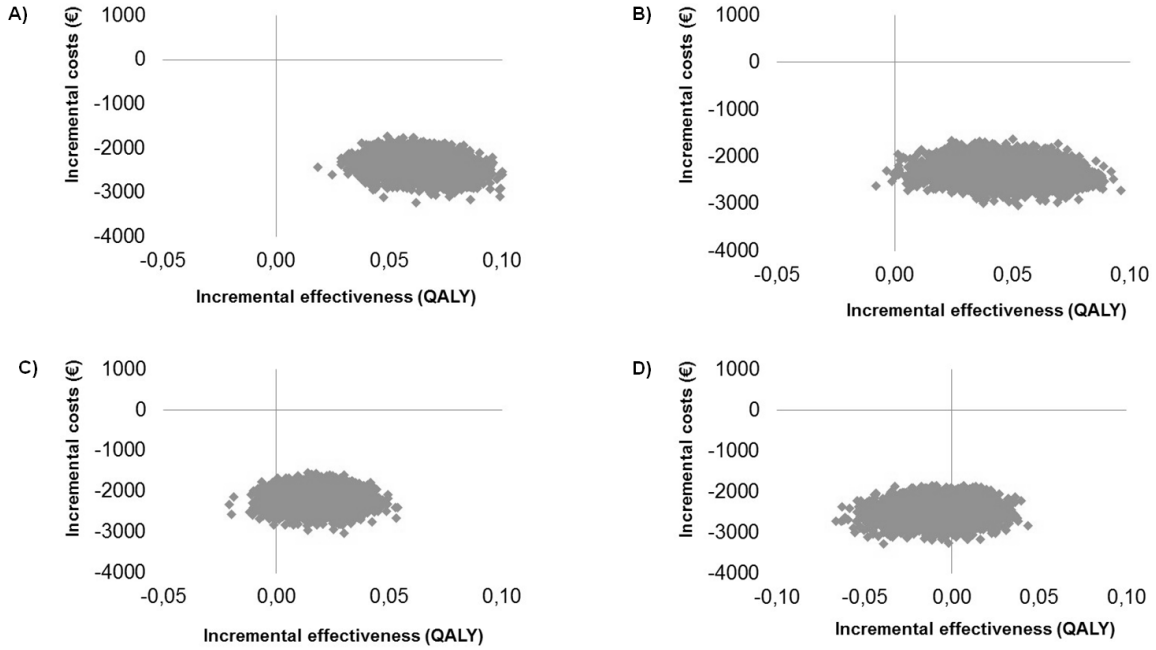
Figure 2 Tornado diagrams of one-way sensitivity analyses on net costs and net QALYs for A) male users of telephone service and B) male users of chat service



Light-coloured bars show the result in case of a minimum value on the parameter; dark-coloured bars show the effect in case of a maximum value on the parameter. Values were varied with ±30%. Relative range in values is shown between brackets.

Prev.: Prevalence

Figure 3: Cost-effectiveness planes for: (a) male users of telephone service (b) male users of chat service (c) female users of telephone service (d) female users of chat service



DISCUSSION

Telemedicine for suicide prevention purpose, like the Flemish suicide helpline, empowers individuals by providing accessible prevention services. This cost-effectiveness analysis has shown that the suicide helpline in Flanders leads to a small gain in QALYs and cost-savings for the health care payer as well as for society at large. The dominance of the helpline is most clear for male users of the telephone service, not because of the service itself (as the same relative risk reduction occurred with both the telephone- and the chat service) but because the risk of committing suicide is higher in adult males than females (23.5/100,000 versus 8.3/100,000 (Vlaams Agentschap Zorg en Gezondheid, 2012b)). The model estimated that over ten years the helpline can avoid about 36% of suicides and suicide attempts in males as well as females. A budget impact analysis revealed important savings for the public health service. For each euro invested in the suicide helpline, the national health insurance gains almost €7 especially by means of the telephone service. The greater societal savings in an average female user of the chat service in comparison with a female user of the telephone service can be explained by the fact that the direct medical cost of an attempt is higher than the direct medical cost of suicide (€2,933 against €2,600 respectively). As productivity costs were only assigned to the age categories between 20 and 60 years, there are a lot of females in the chat service group (whose mean age is 21 years) who do not bring along productivity costs. Since more attempts than suicides are prevented in the chat service group (in absolute figures), especially in females, this can explain the higher savings due to the chat service compared to the telephone service in females. In males, the ratio between avoided attempts and avoided suicides is smaller. On the other hand, the greater societal savings in male users of the telephone service in comparison with female users of the telephone service can be explained by the fact that males are more likely to commit suicide than females and that older people are more prone to commit suicide than younger people (Vlaams Agentschap Zorg en Gezondheid, 2012b).

The QALY impact of the suicide helpline was rather small. The lower gain in QALYs for the chat service than for the telephone service was due to the fact that more suicides are prevented in the telephone group, since this group contains older people (mean age 42 years) than in the chat service group (mean age 21 years), who are more likely to commit suicide than younger people. As preventing suicides leads to the highest gain in QALYs, this can explain the difference between the chat- and telephone service group. On the other hand, males gain more QALYs than females because males are at higher risk to commit suicide than females. It is clear that differences in the telephone service and chat service concerning health gains and cost-savings are due to the demographic and suicidal characteristics of the helpline users. These characteristics also explain the fact that the helpline did not have an effect on the quality of life in female users of the chat service.

To validate our results, the model has been subjected to comparison with suicide probabilities in other scientific literature. In our model, there is a risk of 29.4% in the telephone service group and 37.4% in the chat service group of ever making a first suicide attempt in 10 years. In Kessler, Borges & Walters (1999) the lifetime probability of making an attempt was 37.9%. In Zahl & Hawton (2004) patients who already made a first attempt were followed for an average of 11.4 years. Of them, 2.6% committed suicide, 89.7% remained in the follow-up state, and 7.7% died from other causes. In our model, the distribution over the states after 10 years is as follows: 2.34% (telephone service) and 1% (chat service)

committed suicide; 12.3% (telephone service) and 13.2% (chat service) made a first attempt ever in those 10 years; 1.6% (telephone service) and 1.8% (chat service) ever made a re-attempt; 55.8% (telephone service) and 62.3% (chat service) were or still are in the follow-up state; 25.9% (telephone service) and 21.4% (chat service) have remained in the initial state and 2.1% (telephone service) and 0.3% (chat service) died from other causes.

Some international research about the effectiveness of suicide prevention interventions has already been carried out, although most of the studies were of poor methodological quality (Scott & Guo, 2012). Since there is a scarcity of health economic evaluations of suicide helplines and since there are a lot of differences in analysis methods and assumptions, comparison of our results with other national or international studies is difficult. Many researchers, including ourselves, conclude that a great deal of research remains to be done on the cost-effectiveness of suicide prevention interventions (Kirkwood, Stamm, Hudnall, & Blampied, 2010; Krysinska & De Leo, 2007; Mishara & Daigle, 2000). However, Sari et al. (2008) and Zaloshnja et al. (2003) showed that some suicide prevention interventions have favorable cost-to-benefit ratios. The present study had certain limitations. First, the relative risk reduction included in our study was derived from an American suicide helpline (Gould et al., 2007) which resembled the helpline in our analysis. However, there is uncertainty in this parameter, as Gould and his colleagues did not make use of a control group in their study. Second, the length of one cycle in our model is one year. In reality it is possible that an individual makes an attempt and a re-attempt in the same year. Hence, in our model, the re-attempt will be postponed, which may bias the results in favor of our suicide helpline. Third, relative incidence rates for suicide in suicidal persons and for re-attempts were not available for Belgium, so information from the U.S. (May et al., 2012) and Spain (Tejedor et al., 1999) was used. Fourth, an annual cost of suicide per patient was not available in Europe, so we had to make use of data from the U.S. although the U.S. has a very different health care system. Fifth, the model was based on some assumptions in the literature concerning age-related incidences (Corcoran, Keeley, O'Sullivan, & Perry, 2004; Scoliers, Portzky, van, & Audenaert, 2009). Re-attempt incidences were not specified for different age-groups so calculations were based on the assumption that the relative age-dependent incidences of attempts in the Flemish population were also applicable to re-attempts. The same assumption was applied to calculate age-specific utilities. The age-distribution of the utilities for general health was used to make other utilities age-adjusted. A strength is that information specific to the target group was obtained to build the model. This leads to more accurate outcomes. Finally, the Markov model depended on age, gender and medium and every age-category, gender and medium had its own state transition probabilities.

CONCLUSION

The present cost-effectiveness study suggests that both the telephone- and the chat service of the Flemish suicide helpline may lead to cost savings as well as small health benefits (especially for adult male users of the telephone service) over a period of ten years. Differences concerning health gain and cost-savings between both services were mainly due to the characteristics of the users. The budget impact shows that the helpline also has great annual benefits for the public health service. Both the

telephone- and chat service of the suicide helpline are therefore likely to be cost-effective for suicide prevention in Flanders and should be continued. More suicide research is necessary mainly on the effectiveness of the Flemish suicide helpline in reducing the suicidal state of the person.

Part 3: General discussion

3.1. Introduction

Although cost-effectiveness analysis is mainly used to evaluate clinical health care interventions, it has potential for evaluating public health prevention interventions as well. However, the use of cost-effectiveness evidence in policy, especially of public health prevention interventions, has been estimated to be limited. This is mainly due to the availability, quality and transparency of such evidence, the clarity of its presentation and the extent to which policy makers understand such analysis.

The first aim of this PhD-thesis was to assess the cost-effectiveness of 8 public health interventions in the continuum of prevention, that hold some promise to reduce the health burden at a reasonable or lower total cost. These findings will be summarised below in section '3.2.1. Health economic results'. The second aim of this PhD-thesis was to inform researchers as well as policy makers on the interpretation of cost-effectiveness results and the use of such information by reporting and reflecting on the main uncertainties that were encountered in the included cost-effectiveness analyses. In section '3.2.2. Main methodological challenges', we discuss the uncertainties that frequently emerged while performing the cost-effectiveness analyses and while interpreting the results. In the third section of this discussion part, the use of the study results is discussed in light of the uncertainty and in the final section, recommendations for research practice, publich health practice and policy are proposed.

3.2. Main findings and discussion

3.2.1. Health economic results

Universal prevention interventions: the ToyBox-intervention and skin cancer prevention

The first intervention, classified as universal prevention, was the ToyBox-intervention, aiming to prevent obesity in pre-schoolers. The ToyBox-intervention led to less screen time during weekdays and a lower total sugar-sweetened beverage consumption in pre-schoolers. Considering a willingness-to-pay threshold similar to the GDP per capita of the particular country, the intervention was shown to be cost-effective in Spain for males and females (ICER of €21,719/QALY (95%CI €2,646 - €178,296/QALY) in males and €10,568/QALY (95%CI €476 - €87,298/QALY) in females) and in Polish females (ICER: €6,304/QALY (95%CI €1,277 - €44,637/QALY). The probability of the ICER to be below the assumed threshold was 85%, 78% and 73% respectively. In Belgian and Greek females, the intervention was borderline cost-effective, with a probability of 43.2% and 37.3% for the ICER to be below the threshold. Results were generally better in females than in males, mainly because tracking of obesity from childhood into adulthood is stronger in females (Venn et al., 2007). This resulted in the relative risk reduction in adult overweight and obesity, based on the intervention effect, being larger in females. The probability of the intervention being cost-effective was the lowest in Bulgaria and Germany. This is probably due to the intervention cost which was high in Germany (€29,325 per 1,000 pre-schoolers), but also due to the willingness-to-pay threshold which was very low in Bulgaria (€5,650/QALY gained). Additionally, it was shown that when the intervention effect would sustain longer than the assumed one year, the cost-effectiveness results would be better. The key parameters influencing the cost-effectiveness result were the parameters related to the causal chain of the model design, the intervention

cost and –effectiveness and the incidence of diabetes. Sensitivity- and scenario analyses stressed the need for more research on the relation between child health behaviour and weight status, or even better, between child health behaviour and adult weight status or adult risk on obesity-related diseases. More information is also needed on the sustainability of the intervention effect of the ToyBox-intervention, but also of similar interventions in general, in order to simulate the long term effects of such prevention interventions.

The second study assessed the health and economic burden of skin cancer currently and in the future, in order to investigate the need for prevention. The cost-effectiveness and budget impact analysis evaluated the impact of prevention on this burden. Two hypothetical universal prevention interventions were evaluated, namely a comprehensive sensitisation campaign and a total ban on sunbed use. Results of the burden of skin cancer analysis estimated a current prevalence of about 140,000 skin cancer diagnoses. This prevalence was estimated to triple in the coming 20 years, based on a rising trend in incidence and on ageing of the population. The cost per skin cancer type and stage per six months was assessed by means of a retrospective bottom-up cost analysis. The current annual total cost of skin cancer (i.e. cost for detection and diagnosis, treatment, follow-up and productivity costs of MSC, BCC and SCC patients in 2014) in Belgium was estimated to be €107 million of which the greatest part is funded by the public health care payer. The cumulative cost in the next 20 years was estimated at €3.2 billion. Results of the cost-effectiveness and budget impact analysis of a hypothetical sensitisation campaign or a total ban on sunbed use in Belgium showed that both interventions are predicted to lead to a gain in QALYs and to be cost-saving on the long term. Implementing one of both strategies would save on average €155 million on the long term for the public health care payer. The return on investment associated with the implementation of a sensitisation campaign was estimated at €3.6 per euro invested. Main influencing parameters were the effect of the campaign on sunburn, the relative risk on skin cancer in case of sunbed use, the utility related to skin cancer, the incidence of skin cancer and the medical costs due treatment of advanced MSC. Higher values on these parameters resulted in higher cost-savings.

Selective prevention interventions: population-based screening program for colorectal cancer, breast cancer and skin cancer

The cost-effectiveness analysis of the breast cancer screening program in Flanders (with a biennial mammography for women aged 50-69y) predicted the screening to gain QALYs, by a reduction in breast cancer mortality of 14% and a reduction in the incidence of breast cancer stage IV by 14%, in reference to no screening program. The result of the budget impact analysis showed that the screening program led to a net cumulative cost of €492 million over 20 years. Despite the extra cost, the probabilistic ICER was €31,377/QALY gained (95%CI: €21,973 – €54,977/QALY gained), with an 83% probability of being below the threshold.

The cost-effectiveness analysis of the colorectal cancer screening program in Flanders (with a biennial faecal immunological test for persons aged 56-74y) showed that, over a period of 20 years, the program was predicted to increase the total quality of life in the population aged 50+, due to a decrease in CRC

mortality by 21% and a reduction in the incidence of invasive CRC by about 24% (as all detected polyps are removed), compared to no screening program. The impact of the screening program on the health care budget, estimated at an extra €118 million over 20 years, was partly compensated for by the health benefits, resulting in an ICER way below the informal threshold of €35,000/QALY gained, namely €1,681/QALY gained (95%CI: €-1,317 – €6,601/QALY gained) in males and €4,484/QALY gained (95%CI: €-3,254 – €18,163/QALY gained) in females. The probability of the screening program being cost-effective was 100% and 97.3% in males and females respectively.

A one-time total body examination (TBE) as well as a one-time lesion-directed screening (LDS) were both predicted to gain a small amount of QALYs in the total population on the long term, by means of a stage-shift from more advanced to less advanced lesions and a predicted relative mortality reduction of 5% in case of TBE (i.e. 630 deaths less over 20 years). Due to the screening cost and the extra costs for treatment and follow-up, implementing the screening strategy would induce an extra €36 million in case of TBE or €6 million in case of LDS for the public health care payer, over a period of 20 years. Nevertheless, the balance between costs and health effects was shown to be below the threshold of €35,000/QALY gained, although in the case of males both screening strategies tended to this threshold limit (€31,360/QALY gained (95%CI: €23,251 – €41,468/QALY gained) in TBE and €34,170/QALY gained (95%CI: €25,586 – €44,831/QALY gained) in LDS). The probability of TBE and LDS being below the €35,000 threshold was 79.7% and 59.9% respectively in males and 100% in females. The cost-effectiveness result was clearly better in females than in males because of the higher prevalence and incidence of skin cancer in females in Belgium. Similarly, the result was better in TBE than in LDS because of the lower participation rate in LDS. Since LDS was less time-consuming for the dermatologist, but produced the same yield as TBE, increasing the participation rate of LDS to the level of TBE would result in LDS being more cost-effective than TBE. Some scenarios from a practical viewpoint were tested, including repeated screening strategies, and showed a one-time screening from the age of 18 to be the most cost-effective strategy, although screening from the age of 40 did not drastically change the results.

Some common main influencing parameters were identified in these four screening strategies, namely the natural progression of cancer, the test-characteristics of the screening test, the prevalence of undiagnosed lesions and the utility related to treatment and follow-up of early-stage tumours. The higher the value of these most influencing parameters found in all studies, the better the cost-effectiveness. One exception was the prevalence of undiagnosed basal cell skin cancer (BCC). If the prevalence of such lesions is higher, then screening would not be cost-effective anymore. Derived from this study, we assume that screening for BCC might not offer good value for money. Screening for BCC does not affect the quality of life, but it does safe some money as treating small BCC lesions is less expensive than treating bigger lesions. However, when there are many BCCs to treat, the costs for treatment and follow-up seem to be too high, undermining the effect of early detection on the cost side. In our study the screening included all skin cancer lesions, but it might be that screening for melanoma only would be more cost-effective. However, from a practical viewpoint, screening only for melanoma lesions is an unrealistic scenario. Some specific influencing parameters per disease area were identified as well. The

adherence to colonoscopy after referral was an important influencing parameter in the study of colorectal cancer, absenteeism due to having a mammography in the study of breast cancer screening and the direct and indirect cost of MSC stages III and IV in the skin cancer screening study.

Indicated prevention intervention: the suicide helpline

The cost-effectiveness analysis of the suicide helpline in Flanders evaluated two services which both aim to reduce the acute suicidal state of the helpline user, namely the telephone service and the more recent chat service. Both services were predicted to reduce the number of suicides and first suicide attempts over a period of 10 years by 36% (33 suicides and 205 attempts). The impact on quality of life was small to absent, and was most noticeable in male users of the telephone service. However, all strategies resulted in cost-savings for the health care payer as well as for society. Differences in the model outcomes of the chat- versus telephone users were due to the profile of the users, as the effectiveness was assumed to be the same for both services. Suicide happens more in males than in females (23.5/100,000 versus 8.3/100,000 respectively), while the prevalence of suicide attempts is higher in females compared to males (182/100,000 versus 143/100,000 respectively). As preventing suicide gains more health benefit and saves more money (mainly due to productivity loss) than preventing an attempt, the suicide helpline is more cost-saving in males than in females. Similarly, the prevalence of suicide is higher in older than in younger persons. Older persons make more use of the telephone service than the chat service, which makes the telephone service more cost-saving than the chat service. These reasons also explain why the chat-service does not lead to a health gain in females. Different scenarios and variation in the value of the parameters showed no big difference in the cost-savings.

To summarise, Figure 7 gives an overview of where the interventions are situated in the cost-effectiveness plane, based on the mean incremental costs and QALYs. Figure 7a shows that all interventions are situated in the east quadrants, showing an increase in QALYs, except for the chat service of the suicide helpline in female users. Some intervention strategies are situated in the south-east quadrant of the cost-effectiveness plane, namely the suicide helpline strategies and the universal prevention strategies for prevention of skin cancer. These are the strategies that were estimated to lead to health effects and cost-savings and are therefore called dominant strategies. The majority of the interventions strategies however are situated in the north-east quadrant (Figure 7b, showing this quadrant enlarged), which means that these interventions induced not only a gain in QALYs, but also extra total costs. However, most interventions were found to have a good balance between the gained health effects and extra costs, leading to an ICER below the assumed willingness-to-pay threshold of €35,000/QALY gained. There was one exception, namely the ToyBox analysis in Belgian males (17% probability of being cost-effective at a threshold of €35,000/QALY gained) and females (43% probability of being cost-effective). This intervention was however shown to be cost-effective in Spain and Poland. Nevertheless, these results should be interpreted in light of their uncertainties, which are described in the next sections.

Figure 7a: Cost-effectiveness plane displaying the incremental cost-effectiveness ratios of all included interventions

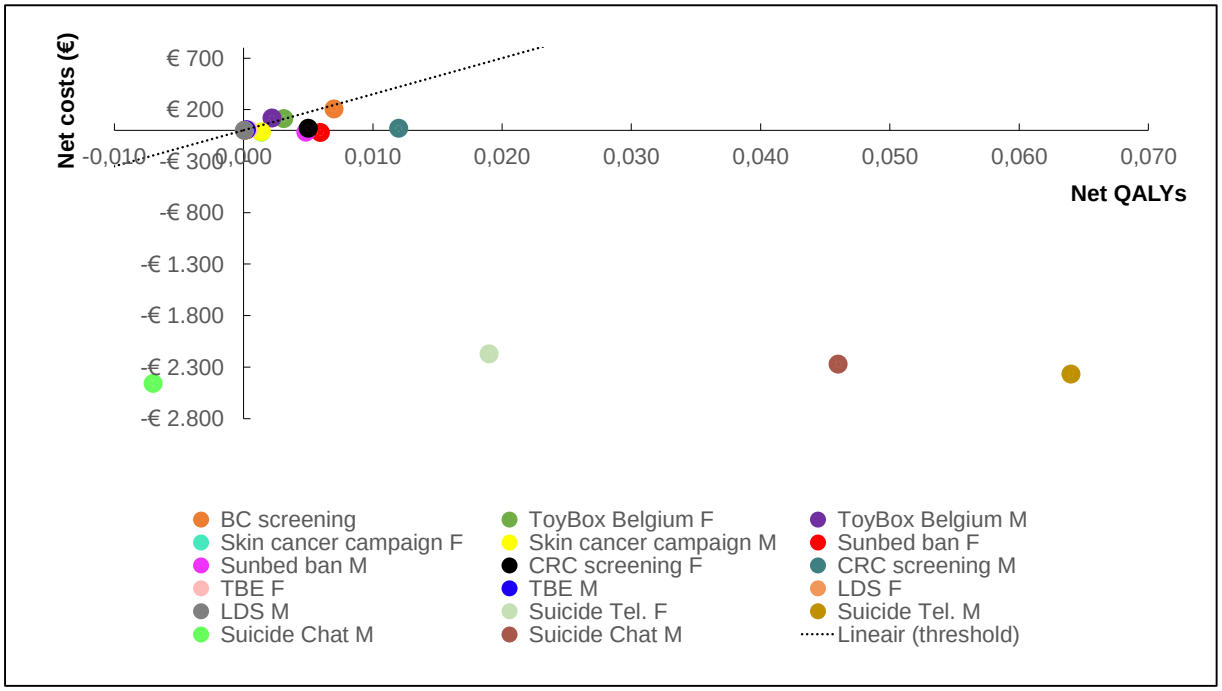
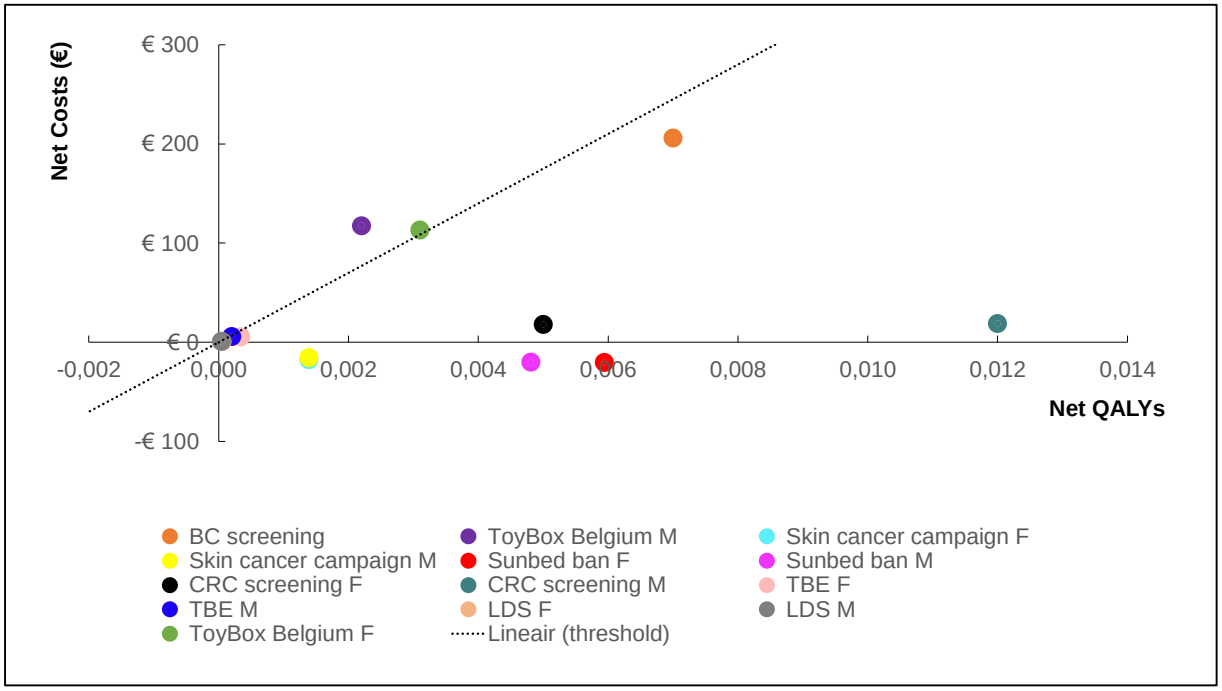


Figure 7b: Enlargement of one quadrant of the cost-effectiveness plane displaying the incremental cost-effectiveness ratios of the included interventions



F: females; M: males; BC: breast cancer; TBE: total-body skin cancer examination; LDS: lesion-directed skin cancer screening; CRC: colorectal cancer

3.2.2. Main challenges

While performing the evaluations included in this thesis, some main challenges have emerged. They will be discussed in this paragraph, classified according to the three main sources of uncertainty in cost-effectiveness research as explained in the general introduction of this thesis, namely structural uncertainty, parameter uncertainty and methodological uncertainty. Some challenges in the use of cost-effectiveness in policy decisions as addressed in the general introduction will be discussed shortly as well. In the following paragraphs the uncertainties we encountered in our studies are described as well as the ways we explored and reported these uncertainties in order to increase the model credibility (marked by paragraph indents).

Structural uncertainty: indirect evidence

All cost-effectiveness studies included in this thesis provided predictions on the long term cost and quality of life based on indirect evidence. Public health interventions often take a long time to demonstrate effect (Drummond, 2007; Kelly, McDaid, Ludbrook, & Powell, 2005; Marsh, Phillips, Fordham, Bertranou, & Hale, 2012; Weatherly et al., 2009). Therefore, studies assessing the intervention effectiveness usually focus on intermediate outcomes which can be observed in shorter time periods (e.g. lower blood pressure, higher consumption of fruits and vegetables, number of cancers detected, prevalence of depressive symptoms...). This brings about two challenges, namely that long term predictions need to be made based on indirect (short term) evidence and that the long term predictions cannot yet be tested based on real-life data. Intermediate outcomes have to be extrapolated to long term final endpoints relevant to health economic evaluations, using a modelling approach. For example in the case of the ToyBox-intervention (Chapter 2.1.1.- 2.1.2.), up to now there are no long term studies showing the impact of a school-based intervention focusing on health behaviours on the onset of chronic diseases in adulthood. In case of cancer screening (Chapter 2.2.), up to now few real-life evidence is available on the impact of screening on mortality and cancer incidence. Some studies have been performed, especially concerning breast cancer, but these show inconclusive evidence, aiming for further research. As it takes a long time before any health effects emerge, such long term studies are difficult to perform, time-consuming, costly and therefore almost impossible. As such, the effect of a public health intervention is commonly indirectly projected to the long term final endpoints by means of a chain of evidence structure (Ades, 2003; Claxton, Sculpher, & Culyer, 2007). Linking intermediate to long term health outcomes may be a more frequent research issue in appraising public health interventions than in conventional economic analyses of health care interventions (Claxton et al., 2007). In the evaluation of the ToyBox-intervention (Chapter 2.1.1.- 2.1.2), an extrapolation was made from childhood health behaviour to the weight status two years later, subsequently from childhood weight status to adult weight status based on tracking studies and finally from adult weight status to chronic disease endpoints. Also the evaluation of the prevention of skin cancer by means of a sensitisation campaign (Chapter 2.1.3.), made use of an intermediate endpoint. The prevention campaign was modelled to have an impact on skin cancer incidence through the effect on sunburn. The long term health effect of the screening programs evaluated in this thesis (Chapter 2.2.) was modelled through early detection of lesions leading to a stage shift in the cancer epidemiology from more severe lesions to less severe lesions. Because of this stage shift, a mortality reduction and increase in quality

of life is expected. The cost-effectiveness study of the suicide helpline in Flanders modelled the effect on attempts and suicide, through the effect on the prevalence of severe suicidal thoughts (Chapter 2.3.1.). Hence, all studies included a causal chain of evidence, the one being longer and more complex than the other, to establish how a public health intervention causes an outcome and to predict the population health outcome resulting from an intervention (McDaid et al., 2008; Threlfall et al., 2015). Despite their usefulness in modelling studies, such causal chains create uncertainty. The length of this causal chain between interventions and outcomes was described as one of the key challenges for economic evaluations of public health interventions (Kelly et al., 2005; Kelly et al., 2010; McDaid, Sassi, & Merkur, 2015). Providing indirect evidence on the long term is based on modelling assumptions which can influence the cost-effectiveness result and thus lead to different policy decisions (Drummond & Sculpher, 2005). The more indirect relations included in the model, the longer the causal chain and the more uncertainty incorporated in the model.

All models used for the evaluation included in this thesis have been constructed with or revised by clinical experts in the field to assure the model includes all aspects of reality considered important by experts. The model should represent reality as simply as possible, while capturing underlying essentials of the disease process and interventions (Eddy et al., 2012). This process increased the face validity of our models, including the causal chain.

In order to validate the causal chain internally, we verified individual equations to make sure that all the calculations included in the causal chain were performed correctly. An example of such verification is extreme value analysis, such as erasing the intervention effect, assuming all utilities to be the same, using sensitivity analysis to detect illogical changes in the result when varying input parameter values, etc.

Furthermore, uncertainty in the main building blocks of the causal chain, namely the linking parameters, was tested by one-way sensitivity analysis. In the ToyBox-analysis (Chapter 2.1.2), it was shown that the link between the weight status of the pre-schoolers and the mid-term weight status based on the health behaviour was one of the most important influencing parameters. Also the tracking parameters and the relative risk of obesity on the incidence of obesity-related diseases had a main influence on the results. Stronger causality would have led to better cost-effectiveness results. In the case of the skin cancer sensitisation campaign (Chapter 2.1.3.), it was shown that the influence of the campaign on the prevalence of sunburn had an impact on the result, but it did not change the conclusion. The result remained cost-saving and was robust for change in this parameter. Finally, we want to mention that already validated models may exist to investigate a particular research question. For example, in the case of cancer screening some models have been built and thoroughly validated, such as the models from the seven research groups in the Cancer Intervention and Surveillance Modelling Network (CISNET) to evaluate cancer control interventions. One of these models is the Microsimulation Screening Analysis (MISCAN) model from Erasmus University Medical Center (The Netherlands) (Habbema, van Oortmarssen, Lubbe, & van der Maas, 1985; Loeve, Boer, van Oortmarssen, van, & Habbema, 1999). However, to use the models built by these research groups is expensive and it is not clear to what extent all complex mathematic calculations are transparently described for every researcher to be used.

Parameter uncertainty: data input

A second and related important challenge that we faced in our studies was parameter uncertainty. Parameter uncertainty generally arises in two ways. Firstly, there is uncertainty due to sample variation around the parameter estimates and secondly, there is uncertainty on which input values to include, and where to find the information on the parameter estimates. It is this second type of parameter uncertainty that is addressed in this paragraph. In all studies we faced a lack of detailed data. The type of missing data depended on the different types of studies. For example, in Chapter 2.1.2, the cost-effectiveness of the ToyBox-intervention was evaluated in six participating countries. As such, this analysis required international data. Data concerning the costs and quality of life related to an obesity-related disease and the incidence of such diseases was not always available and had to be imputed. In Chapter 2.1.3., the aim was to evaluate the cost-effectiveness of a hypothetical comprehensive skin cancer sensitisation campaign in Belgium. Although small and fragmented campaigns have been implemented in Belgium, no effectiveness data is available. Alternatively, we had to rely on published effectiveness data in other countries. Unit costs and health effects of skin cancer in Belgium have recently been investigated (Tromme, 2015; Tromme et al., 2014). However, these data only included melanoma and as new expensive treatment options have emerged in the last years, we apprehended these data to be outdated. Therefore, patient questionnaires were composed in order to assess health care consumption, drug use, quality of life and impact on the job situation of patients with BCC, SCC of MSC. These questionnaires were completed by 287 Belgian skin cancer patients. However, this is a time-consuming exercise (and even then not including a sufficient number of patients) which was not always possible to perform in the other evaluations included in this thesis. For example, in the case of the suicide helpline analysis (Chapter 2.3.1.), we had to rely on published data from the U.S. for the medical cost due to suicide. The cancer screening studies (Chapter 2.2) faced some similar caveats in the data inputs. Firstly, there was a lack of data mainly concerning the natural progression of the tumours. Secondly, the epidemiology of adenomas (in the colorectal cancer screening model) and non-melanoma skin cancer in Belgium/Flanders is currently unknown. However, as there are plans to start a colonoscopy register in Flanders, there should be more information on the epidemiology of adenomas in the future. Currently, these data were based on a German adenoma study (Brenner, Altenhofen, Stock, & Hoffmeister, 2013; Brenner et al., 2014). Non-melanoma skin cancer rates were derived from the Dutch cancer registry (Integraal Kankercentrum Nederland, 2011), as, in contrast to Belgium, in the Netherlands these tumours are systematically registered. However, these data only included the first lesion, which could have affected our results.

Consulting (clinical) health experts was not only relevant to validate the structure of the model but also to discuss the best available data sources. Uncertainty in data input was mainly tested by one-way as well as probabilistic sensitivity analysis. The one-way sensitivity analysis revealed the impact of the uncertainty in the particular parameters by varying the value of these parameters. The probabilistic sensitivity analysis showed uncertainty in the parameters by creating credibility intervals around the mean ICER estimate.

In the breast cancer screening model (Chapter 2.2.1.), the natural progression was calculated by means of a Poisson regression analysis, based on estimates from Tan et al. (2013). In the

colorectal screening model (Chapter 2.2.2.), the natural progression rates were derived from the study of Hur et al. (2007) who calculated these rates based on calibration with the observed stage distribution. Also in our model, the estimated stage distribution approximated the observed stage distribution, so the progression rates as estimated by Hur et al. were adopted in our model. Natural progression rates for skin cancer (Chapter 2.2.3.) were calibrated based on the estimated skin cancer deaths in Belgium.

Additionally, some validation checks applied to structure uncertainty as well as parameter uncertainty: (1) the outcomes predicted by the comparator arm in our models (which usually represents the current standard) were compared with observed outcomes (outcome validation). In the cancer screening program analyses the model outcomes were tested according to the observed prevalence and cancer deaths (Chapter 2.2). Comparison of expected cancer deaths according to the model with those observed was only possible in the skin cancer analysis as in the model of colorectal cancer and breast cancer, there were only undiagnosed lesions at the start of the model. In the evaluation of the ToyBox-intervention (Chapter 2.1.2.), the prevalence of obesity-related diseases as predicted by the model based on disease incidence and the transition probabilities was compared to the observed prevalence. Although some slight differences were shown, the predicted outcomes approximated the observed outcomes. In the case of the suicide helpline, outcome validation was more difficult as the target population only consisted of a high-risk group, which could not be compared to the total population (Chapter 2.3.1). As such, prevalence of suicide or suicide attempt could not be compared to the national or regional prevalence. (2) When possible, the predicted outcomes by the intervention arm were compared with the outcomes observed in real-life, in order to test whether the model makes accurate predictions of future events (predictive validation). For example, in case of the screening analyses (Chapter 2.2), the positivity rate predicted by the model was compared to the one observed. However, as stated before real-life data may not always be available at the moment of the analysis, which makes predictive validation difficult. Moreover, as already stated before, long term longitudinal studies are almost impossible to undertake because of the long term that needs to be bridged, which makes it costly, time- and energy consuming and difficult to control for other factors that can affect the outcome (Edwards, Charles, & Lloyd-Williams, 2013; Fischer et al., 2013; Kelly et al., 2005; Kelly et al., 2010; Marsh et al., 2012; Threlfall et al., 2015; Weatherly et al., 2009). (3) Also, all outcomes of the original research studies included in this thesis have been compared to other published research studies addressing a similar research question (cross validation). Nevertheless, comparison may be impeded by transferability issues: a great deal of our model inputs are country-specific (such as participation rate in screening), limiting the ability of direct comparison with other studies (see paragraph 3.2.3.).

Furthermore, we want to stress the importance of good quality databases. In 2006, the Belgian Health care Knowledge Centre issued a report with an inventory of available databases in health care (Federaal Kenniscentrum voor de gezondheidszorg, 2006). The conclusion was that Belgium has many registries and databases, collecting detailed data. However, some substantial gaps were identified. Content-wise,

the lack of data on outpatient treatment, about technology used in health care and non-reimbursed health care consumption were addressed. Concerning the practical organisation, the fragmentation of the databases was denounced, as well as the accessibility of the databases to secondary users, which is hampered by legal conditions and procedures such as privacy laws. Anno 2016 these gaps are still present. There is need for centralisation of clinical patient data and for linking databases in order to create integrated databases (Camberlin et al., 2013). Such databases could contain not only clinical data such as the diagnosis, but also resource use, costs and demographic information. Although there are some initiatives to integrate data, such as linking data from the Intermutualistic Agency[15] and the Belgian Cancer Registry (Camberlin et al., 2013; Maetens et al., 2016), more initiative on the linking of databases could be useful for scientific research. The Belgian government recognises these needs. In the coalition agreement of the federal government (2014) the development of an efficient data system is recognised as an objective. The goal is "developing a centralised health information system that fills the gaps in the knowledge landscape and coordinates the registration and management of data, ...". An e-Health action plan 2013-2018 was agreed upon, which involves a cooperation agreement between the federal government and the regions. This includes among other things the development of streamlined data registration and exchange between states, but also the (re)-evaluation of existing financial incentives for data-processing of health care providers. An additional important plan is to work on a legal basis for obtaining anonimised aggregated data for public and private research purposes.

Methodological uncertainty: Choice of methods

Methodological uncertainty relates to the methodological choices that need to be made. The methodological choices we encountered were mainly associated with technical aspects of an analysis, such as what health effects to include, what perspective to take, how long the time horizon should be and the duration of the intervention effect. Equity issues are also described in this section.

A. Health effects

The most challenging question on what effects to include in our analyses was not about the health effects but rather about the harms that could emerge by the intervention. Public health interventions aim to deliver an overall population health gain. Thereby, it seems to be accepted that some individuals will not benefit, or may even experience a degree of harm. However, lately there has been a lot of debate concerning the negative aspects of population-based screening. As stated in the review of Koleva-Kovarova et al. (2015), most screening models only include health benefits. To address this issue, we tried to incorporate some disadvantages of screening in our analysis (Chapter 2.2). As such, we included the possible impact of a false-positive screening result on quality of life in terms of psychological harms in the screening models (Cullen et al., 2004). Anxiety that could possibly be induced by the screening invitation was not included, as this has not yet been explored in currently published research. The risk of overtreatment (and associated costs and health effects) was implicitly included in the model, as it was assumed that all detected lesions were treated. Risk of radiation-induced breast cancers due to the

[15] The Intermutualistic Agency is an instance collecting and analysing administrative data from the seven Belgian health insurers. This agency does not dispose of medical patient data.

mammographic screening program was not included in the model, since other studies have shown this risk to be very small (Hauge et al., 2014; Yaffe & Mainprize, 2011). The risk of bowel perforation or bleeding as a consequence of a colonoscopy, is implied in the cost estimates (derived from Pacolet et al. (2011)). Capacity constraints, impeding tests or examinations to be performed immediately after one another, were included as the period patients are assumed to experience a disutility due to a false positive result. It should be noted that there was a problem of waiting times in the first year after enrolment of the colorectal cancer screening program (Vlaams Agentschap Zorg & Gezondheid, 2014), but now these waiting times should have declined to a minimum. Including negative aspects is especially important when assessing wide-range interventions (such as universal or selective prevention interventions), as these interventions reach a lot of persons and can therefore induce potentially large harms.

By means of a scenario-analysis the effect of using different values for the disutility due to a false-positive screening result was tested. For example in the analysis for breast cancer screening, it was shown that the worst case scenario for the utility associated with a false positive result, i.e. equal value to the utility associated with a detected stage I breast cancer lesion, would have a high impact on the cost-effectiveness result. The ICER would deteriorate from about €28,000/QALY to €86,000/QALY, which shows the importance of including this potential harm and the need for more research on this topic. When varying the utility associated with a false-positive result in the study of colorectal cancer screening, to the utility of detected CRC stage I, no gain in QALYs in females was realised anymore. From our research, we conclude that more research should be performed on these negative aspects of screening in order for researchers to include them in the cost-effectiveness analysis, as it has been shown that these disadvantages can have a great impact on the cost-effectiveness result.

Another possible harm of prevention interventions is stigma. Health professionals try to achieve that health risks and unhealthy behaviour is perceived as negative, as undesirable (Raad voor Volksgezondheid en Samenleving, 2016) Therefore, it is possible that targeting people with for example obesity, or a mental disorder stigmatises these groups, making them feel inferior and helpless (MacLean et al., 2009). Also, interventions specifically targeting low-income families could be perceived as stigmatising and humiliating. Focusing on promoting health behaviour, instead of a negative focus on unhealthy behaviour could counteract stigma. Stigma is especially a risk of selective and indicated prevention strategies, as such interventions target high-risk groups. Stigma could lead to lower participation rates, decreasing the effectiveness of the intervention or even lead to opposite effects of the intervention. Therefore, public health interventions, as well as the cost-effectiveness analysis, should take this possible harm of stigma into account. In our analyses, we did not take into account the potential harm of stigma due to the intervention, as no information on this topic was available. In case of the ToyBox-study (Chapter 2.1.2.), the risk of stigma could be interpreted as rather small as the positive behaviour was reinforced. However, the content of the sensitising skin cancer prevention campaign (Chapter 2.1.3.) should be screened for stigmatising messages. In case of the cancer screening programs (Chapter 2.2.), stigma in the high-risk groups receiving an invitation could lead to a lower

participation rate. However, currently there is no information on this topic. In case of the suicide helpline, stigma might have led to the fact that persons feeling stigmatised do not make use of the helpline, although the presence of such a helpline should not be stigmatising itself as it is anonymous. Hence, more research is necessary on the stigmatising level of public health interventions, how to measure it, and how to take this into account in the cost-effectiveness analysis.

In addition, it needs to be mentioned that the QALY-outcome does not measure all potential health effects. What about shame (eg. in skin diseases), dignity (eg. Incontinence), sleep deprivation,…?. Another limitation of the QALY-outcome is that it does not capture the costs and benefits of a public health intervention that go beyond the health sector (Drummond, 2007; Edwards et al., 2013; Squires, Chilcott, Akehurst, Burr, & Kelly, 2016; Weatherly et al., 2009). For example, providing a healthy breakfast at school free of charge may not only lead to an improvement in health but may generate additional effects on social and educational development, which are generally not captured by the QALY-concept. Alternative approaches are available (such as cost-consequence analysis, in which all outcome dimensions are prioritised and weighed, or the capability approach[16]), but all have limitations and are not yet used frequently in health economic analyses.

B. Costs

What costs to include in the cost-effectiveness analysis is dependent on the perspective the analysis assumes. A health care payer perspective only takes into account the costs to be paid by the public health care payer whether or not supplemented with the costs for the patient. A societal perspective takes into account other costs outside the health care sector, mainly the costs due to productivity loss. Furthermore, there a two methods to value productivity loss, namely the friction cost method and the human capital method. Both have advantages as well as shortcomings, but we used the friction cost method as this is the most conservative one. The friction cost method assumes that a long term absent employee will be replaced (Koopmanschap & van Ineveld, 1992). Therefore, in case of long term absenteeism or in case of death, productivity loss should only be accounted for during the period it takes to replace an employee (assumed to be 160 days (Hakkaart-van Roijen, 2010), instead of during the total period until the person retires or would have been retired (i.e. human capital method).

By means of several scenario-analyses the effect of using a health care payer perspective or a societal perspective was explored, as well as the effect of assuming the friction cost method or the human capital method. From the scenario analyses, we derived that the incremental cost-effectiveness ratio is usually better if a societal perspective is assumed (see Chapter 2.2 and Chapter 2.3.1.). However in case of the cancer screenings, if productivity loss would be applied to undergo the screening test, then the result would be worse from a societal perspective. In our cost-effectiveness analyses a societal perspective was assumed as this perspective provides a more complete picture. The budget impact analyses however, were performed from the public health care payer perspective in order to estimate the impact on the health care budget. In the analysis of the suicide helpline (Chapter 2.3.1) the result was tested based on both productivity loss valuation

[16] For more information, see Mauskopf et al. (1998) and Coast et al. (2008)

methods. The analysis showed that in the case of the human capital method, the net costs would have been twice as low in males, due to the savings in productivity loss and about one third lower in females. Additionally an extra analysis was performed to evaluate the impact on the result in case the period of absenteeism would be shorter than assumed in the analysis, namely 76 days (Bouwmans, Vemer, Van Straten, Tan, & Hakkaart-van, 2014) due to an attempt, instead of 162 days and 160 days due to suicide (i.e. average friction period (Hakkaart-van Roijen, 2010)) instead of 226 days. Table 5 shows that this adaptation would lead to lower costs due to productivity loss which would results in the net costs per person being halved in reference to the base case. However, the conclusions would not change.

Table 5: Impact on the ICER of the suicide helpline, assuming shorter periods of absenteeism

	Results in users of the telephone service				**Results in users of the chat service**			
	males		**females**		**males**		**females**	
	net QALYS	*net costs*	*net QALYS*	*net costs*	*net QALYS*	*net costs*	*net QALYS*	*net costs*
Base case	0.064	€ -2,366	0.019	€ -2,171	0.046	€ -2,272	-0.007	€ -2,457
Change in prod.loss	0.064	€ -1,239	0.019	€ -1,092	0.046	€ -1,205	-0.007	€ -1,243

C. Time horizon

The question of how long to run the model simulation is important for several reasons. In public health interventions, effects usually only appear on the long term. According to the Belgian guidelines, “the time horizon of the model should be long enough to capture all relevant possible effects on the outcomes” (Cleemput et al., 2012). In this sense, a life-time horizon seems the best option in case of public health interventions. However, a long time horizon inevitably comes at the costs of increasingly uncertain estimates (O'Mahony et al., 2015), as the impact of future trends in epidemiology of diseases and innovation in medical technologies cannot be predicted. Additionally, the longer the time horizon, the greater the effect of discounting on the cost and health outcome, what could underrate the impact of the intervention. On the other hand a long time horizon could lead to an overestimation of the benefits of the intervention.

In the analysis of the ToyBox-intervention (Chapter 2.1.2.) as well as in the analysis of a sensitisation campaign and ban on sunbed use (Chapter 2.1.3.) a long time-horizon was included, because an induction period[17] needed to be taken into account. We assumed the induction period for skin cancer to be 20 years, which means that the impact of prevention on the incidence of undiagnosed skin cancer was only implemented from year 20 on. In the Toybox-study, the intervention effect was extrapolated to the adult age, in that the incidence of chronic diseases was affected by the preschool health behaviour. Consequently, an induction period was implicitly included in the model. Because of these time lags between the implementation of the intervention and expected health effects, the time horizon needed to be long enough to capture those effects. In case of screening, the effect should be notable earlier, therefore the effects were modelled over a time period of 20 years.

[17] The induction period is defined as the period between causal action and disease initiation (Rothman, 1981)

However, in a scenario-analyses this time horizon was extended to 50 years in order to explore the effect on the cost-effectiveness result. This analysis showed that assuming a longer time horizon resulted in a better incremental cost-effectiveness ratio. In the study of the suicide helpline (Chapter 2.3.1) the budget impact was estimated over a period of 10 years, which showed a cost-saving effect. When calculating the return on investment the intervention cost was only included once. However, when we assume this intervention cost to be applied for each cohort in the budget impact analysis, while the benefits in 10 consecutive cohorts are captured, the return on investment would have been lower than described in the study, namely €2.4 instead of €6.7 per invested euro.

D. Duration of intervention-effect

Another time-related issue is the duration of the intervention effect. In the case of the ToyBox-study (Chapter 2.1.2.), as well as the analysis of the suicide helpline (Chapter 2.3.1), no evidence on the duration of the effect was available.

Based on a waning effect found in other early childhood obesity prevention interventions, we assumed the ToyBox-study to be repeated annually in order to sustain the intervention effect. However, in a scenario-analysis, the ICER was explored in case the intervention effect would sustain for two years, meaning that the intervention would only need to be re-implemented every two years. As expected, this had a positive result on the ICER. In the case of the suicide helpline, the intervention effect was also assumed to decrease in time and after five years no continuing effect was included anymore. However, we wanted to explore the impact on the ICER if the helpline would only have a short-term impact. Therefore, an extra scenario was evaluated with an effect during one year instead of five years. The results below in Table 6 show that the gain in QALYs and the cost-savings would be lower. However, the main conclusion would not have changed.

Table 6: Impact on the ICER of the suicide helpline, assuming an effect during 1 year

	Results in users of the telephone service				**Results in users of the chat service**			
	males		**females**		**males**		**females**	
	net QALYS	*net costs*	*net QALYS*	*net costs*	*net QALYS*	*net costs*	*net QALYS*	*net costs*
Base case	0.064	€ -2,366	0.019	€ -2,171	0.046	€ -2,272	-0.007	€ -2,457
Effect helpline 1y	0.019	€ -1,162	0.006	€ -1,148	0.025	€ -1,066	-0.003	€ -1,255

E. Equity

Although tackling inequalities in health is an important goal in many public health interventions, economic evaluations focus mainly on the efficiency of interventions, while equity considerations are rather ignored (Cookson, Drummond, & Weatherly, 2009; Drummond, 2007; Sassi, Archard, & Le, 2001; Weatherly et al., 2009). For example, one feature of a cost-effectiveness analysis is that a QALY has equal weight, regardless of the recipient. Also in our studies included in this PhD-thesis, no equity considerations were included. Total health benefit from an intervention was calculated as the sum of all

QALYs without equity weighting or separation between subgroups based on socio-economic status (SES).

Cookson et al. (2009) proposed some approaches to take into account equity considerations in a health economic evaluation: a review of background information on equity supplementing the cost-effectiveness analysis, a health inequality impact assessment generating quantitative evidence about the impact of the intervention health inequality (e.g. the variation between sub-groups based on socio-economic status, age, gender), an analysis of the opportunity cost of equity to estimate the health sacrifice related to the equity consideration (e.g. QALYs forgone by pursuing the equitable option compared with the QALY maximizing option), and equity weighting of health outcomes, i.e. setting quantitative weights on health gains accruing to different people in different circumstances in order to adjust the health outcome for equity considerations. However, these methods seem not to be frequently integrated in cost-effectiveness analysis (Johri & Norheim, 2012).

There is an example of equity weighting of health outcomes for certain clinical treatments in the UK decision process. Since 2009, the National Institute for Health and Clinical Excellence (NICE) has introduced a rule in their advice to the National Health System (NHS) in order to introduce more flexibility in the decision and to promote access to end-of-life treatments. The advice implies that some treatments may exceed the cost-effectiveness threshold of £30,000 per QALY gained, on the condition that the treatment is intended for patients with a short life-expectancy (less than 24 months), extends the life-expectancy with at least three months in comparison with the current NHS treatment, and applies only to a small patient population. When these conditions are met, the commission considers the effect of giving more weight to QALYs gained in the later stages of terminal illness, assuming that the extention of life is experienced at the same quality of life as a healthy person of the same age, and the size of the extra weight that should be given for the cost-effectiveness of the treatment to fall below the threshold.

Use of cost-effectiveness in policy decisions

As stated in the general introduction of this PhD-thesis, it is not clear to what extent cost-effectiveness is used as a criterion in decisions on public health prevention interventions, although it seems to be used in a limited way. Main pullbacks were the availability of relevant research in a timely manner and the extent to which cost-effectiveness evidence can be understood by policy makers, and the quality and transparency of the evidence (Eddama & Coast, 2008). How to explore and improve the quality and transparency of the evidence has been discussed in the previous sections. The extent to which the cost-effectiveness evidence can be understood by policy makers, is related to this quality and transparency issue. Policy makers often struggle to understand health economic analyses, mainly because of the language, concepts and calculations used in such analyses.

Collaboration with policy makers provided added value in performing the study on breast- and colorectal cancer screening (Chapter 2.2.1 and 2.2.2). From this collaboration with policy makers, we learned that there should be better access to health economic evaluations, but providing evidence alone is not sufficient. We not only made our breast- and colorectal cancer model available for the

engaged policy makers, but also involved these persons in every step of the model composition, such as the input data and model assumptions. In this way, they fully understood the assumptions and calculations made and they can make adaptations in case newer data becomes available. This collaboration also rendered more insight in what is important for policy makers, e.g. on what parameters and outcomes they focus, and what parts of the analysis are the most difficult to understand or to interpret.

As also stated in the general introduction, the availability of relevant research in a timely manner can be improved by evaluating the transferability of study results from one country to another.

Despite the lack of data we encountered (see paragraph 3.2.2.), the models in our analyses used local data as much as possible. The study on the cost-effectiveness of a total ban on sunbed use, included the Belgian prevalence of sunbed use in 2013 (Ipsos Public Affairs, 2013). Costs and quality of life data were obtained by questionnaires from 287 Belgian skin cancer patients. Screening parameters in the study of skin cancer screening were derived from a trial implemented in two Belgian cities. The evaluation of breast- and colorectal cancer screening adopted the design of the screening program in the model. Frequency of screening, as well as the specific screening test (such as the OC sensor FIT test with a cut off value of 75ng/ml) and age range of the target population can vary between countries. In case of the suicide helpline, the prevalence of suicidal thoughts was obtained from the data registered by the 'Centrum ter Preventie van Zelfdoding'. Nevertheless, it is entirely acceptable that cost-effectiveness findings vary by setting as background parameters, such as levels of clinical experience, disease severity and prices, may differ. However, if researchers or policy makers want to transfer our study results to their country, they need to explore to what extent our results are transferable to their current situation.

Not only the transferability of our studies should be questioned, but also of the studies that were used to provide input for our model in case Belgian data was not available. For example, in case of suicide helpline evaluation, important input data from other countries –such as the effectiveness of the helpline and the cost related to suicide- had to be imported as Belgian data was not available. However, the U.S. effectiveness study which provided input for our model concerned a helpline with a very similar organisation and similar target population in terms of prevalence of suicidal thoughts, which increased the transferability of those results to our study. Moreover, suppose the relative risk reduction in suicidal thoughts would not 41% but only 20%, the Flemish suicide helpline would still be dominant (althought the cost-savings would be halved). If the effectiveness would be higher than 41%, the cost-savings would logically be higher. In this respect, adopting the effectiveness of the suicide line from the U.S. study has no major impact regarding the conclusion of our study, i.e. that the Flemish suicide helpline is a dominant intervention. Moreover, it is expected that the effect of the U.S. helpline is underestimated because the persons with the strongest suicidal thoughts were not included in the study because during such a call no attention was given to the risk assessment. Additionally, the effectiveness of a public awareness campaign for the prevention of skin cancer was based on the effectiveness of the Australian SunSmart campaign. Although the epidemiology of skin cancer in Australia differs from Belgium and their skin cancer prevention already has a long history,

we adopted this effectiveness measure in relative terms (relative risk) and from the first years it was implemented. A German study evaluating the effectiveness of skin cancer information campaigns during the last 16 years found a relative risk reduction of 32%, which is lower than the 41% found by the SunSmart campaign. This uncertainty was included in the sensitivity analyses and it was shown that the effectiveness of the campaign was one of the main influencing parameters. However, even in case of a lower effectiveness, the intervention was shown to be still cost-saving.

3.3. Interpretation of study results in light of uncertainty

Cost-effectiveness analyses contain inherent uncertainties, which are normal and not completely avoidable. It is always the aim to reduce the degree of uncertainty and especially to explore and describe the uncertainty in the ways mentioned before. As researchers, we perform the cost-effectiveness assessment and give advice, but the final decision is to be made by the policy makers. As such, it is up to the policy makers to decide –based on the cost-effectiveness result but also on other criteria, see general introduction- whether the particular prevention intervention should be implemented (and reimbursed) or not. That is why researchers need to report in a transparent way, describing the uncertainties in the model and the impact of uncertainty on the result. In this section, we interpret the study results described in 3.2.1., in light of the uncertainties described in 3.2.2.. Which study results do show strong evidence and which results should be interpreted with more caution?

As was shown, the analysis of the ToyBox-intervention includes quite a large level of uncertainty. The main uncertainties were related to the extrapolation of the effects from childhood to adulthood, and the duration of the intervention effect. This study should therefore be interpreted as a push for more research concerning these uncertainties and an introduction to similar cost-effectiveness research in pre-schooler obesity prevention interventions.

The study of universal prevention of skin cancer comprised two parts, first an estimate of the number of skin cancers in 2014 and 20 years later, along with the cost of cancer in Belgium in 2014 and 20 years later, and secondly the cost-effectiveness analysis of two universal prevention strategies. The information on the prevalence and costs were based on the skin cancer epidemiology in Belgium and the Netherlands and the annual trend in incidence shown in published literature. Information on the health care consumption of skin cancer patients was obtained from a Belgian patient population through own data collection. The results of the first part contain useful information on the trend in skin cancer and the increase in the number of skin cancers and as such the associated cost, showing the need for skin cancer prevention. With the information from the second part of the study, we have to be more careful since it concerns two hypothetical prevention strategies in Belgium. With this analysis, we particularly wanted to demonstrate the cost-effectiveness potential of these universal cancer prevention strategies in terms of health and financial terms. As these are hypothetical interventions, it is advisable to first conduct further research on what the effectiveness of such measures is or may be in a Belgian context. Especially the sensitivity analysis in this study was highly informative as it showed that the incidence of melanoma plays a role in the cost effectiveness of such strategies. The higher the

incidence, the more cost-effective prevention is. If we expect an increase in the number of skin cancers (based on an estimates from the first part of the study), we can assume that prevention will become even more beneficial. Also, the higher the cost of treatment for melanoma, the more cost-effective prevention becomes. The latter is particularly useful in light of the new, more expensive treatments that recently entered the market.

The next two studies include the cost-effectiveness analysis of the population-based screening programs for breast cancer and colon cancer in Flanders. As these screening programs are already implemented, the screening-related data could be used in the analysis. Based on the results of these two studies and similar studies in literature, we concluded that the current screening programs are cost-effective and should be continued. However, further research is needed on the long-term impact of screening on mortality and the incidence of new tumours (in the further stages), in order to verify whether the model predictions are correct.

A one-time skin cancer screening was shown to be a cost-effective strategy, especially in women; a total body examination showed a slightly better result on cost-effectivenss than the lesion-directed screening (which was only due to the participation rate). However, more information on the natural progression of skin cancer as well as a systematic registration of NMSC lesions in Belgium would improve the cost-effectiveness research. By means of this study we were able to make recommendations for skin cancer prevention in the future, though more research on skin cancer screening to confirm our results (and the most efficient target group and screening interval) is desirable.

Concerning all three cancer screening interventions, it should be stated that further research should also inform on the possible negative effects of screening, for example, the emotional distress of a false positive result and lost work time due to the screening. Currently only few articles report very general on emotional distress because of screening. More knowledge on this topic is important as negative effects of the screening could worsen its cost-effectiveness. The largest uncertainty in the study of the suicide helpline was the lack of information on the effectiveness of the suicide helpline in Flanders and the lack of information about the cost of a (fatal) suicide attempt. On the other hand, based on the results of the sensitivity analysis, we can say that the Flemish suicide helpline is a cost-effective, and even dominant strategy. However, if we want more clarity on the magnitude of the cost savings, it is necessary first to have more information on the effectiveness of the Flemish suicide helpline and the cost of a (fatal) suicide attempt in Flanders/Belgium.

3.4. Recommendations for future practice

In this PhD thesis, we tried to stress the promise and relevance of health economic evaluations of prevention interventions in public health for managing and controlling the health care budget. A variety of interventions in the continuum of chronic disease prevention have been evaluated during this research. All but one intervention showed cost-effective results, and some were even dominant. This shows that (1) public health prevention interventions can have a positive influence, not only on population health but also on the health care budget and (2) that even those interventions that lead to a total extra cost for the health care payer, can still be cost-effective and should be considered in policy

decisions. The included cost-effectiveness studies shared some main challenges, some being specific to the field of public health prevention interventions, such as providing indirect evidence, the choice of time horizon, duration of the intervention-effect, and some being related to cost-effectiveness analysis in general, such as the lack of data, choice and valuation of costs to include, harms of the intervention, etcetera. By our research we informed reseachers, health professionals and policy makers on the uncertainties related with these challenges, by exploring the impact they can have on the cost-effectiveness result. In this way, we stressed the importance of sensitivity analyses and validation efforts, as well as the importance of transparency. Based on the findings in this PhD-thesis, we formulate some recommendations for researchers and health professionals as well as policymakers.

3.4.1. Recommendations for researchers performing cost-effeciveness analyses

Based on our studies included in this PhD-thesis, some recommendations can be made for researchers performing cost-effectiveness analyses in order to increase the quality as well as improve the use and interpretation of cost-effectiveness results for other researchers, health professionals and policy makers. First of all, researchers performing cost-effectiveness analyses should be aware of the uncertainty frequently faced in performing such analyses. Cost-effectiveness analyses of public health prevention interventions often provide indirect evidence. Researchers should analyse the main building blocks of the causal chain providing the indirect evidence and describe the uncertainty associated with those building blocks. Parameter uncertainty is a second main challenge. Solutions to lack of data could be collecting own data, statistical imputation of data or imputation of data from other countries. Besides, not only the positive health effects of prevention interventions should be included in the cost-effectiveness analysis; researchers should also include potential harms of the intervention in the analysis. Furthermore, methodological choices such as the duration of the intervention effect, the perspective of the analysis, the time horizon of the model etcetera should be adressed and explored. Additionally, the uncertainties induced by those challenges should be examined. This can be done by performing one-way and probabilistic sensitivity analysis as well as scenario-analysis.
In order to increase the quality of a cost-effectiveness analysis, researchers need to improve the transparency by clearly describing the model structure, parameters values, assumptions and calculations included in the modelling analysis so that interested parties are able to understand the key drivers of the model, as well as strengths and limitations of the analysis. Transparent analyses are easier to understand, which increases the value and the use of the analysis for other researchers and health professionals and which increases the likelihood of policy makers to make use of the cost-effectiveness information provided by the analysis. Reporting validation efforts is desirable to assess the validity of the model, in order to increase policy makers' and other stakeholders' confidence in the analysis and its outcomes. Researchers should be aware that mean (base case) cost-effectiveness results provide relevant information, but results from sensitivity analyses and model validation exercises are even more informing.

Moreover, in order to enhance the recognisability and uptake of cost-effectiveness evidence from prevention interventions by health professionals as well as policy makers, researchers should cooperate with relevant stakeholders, before, during or after performing the analysis. This could be achieved by

selecting a stakeholder group, representing clinical and health economic experts as well as data registries and policy makers where possible. This group could provide advice on the model structure, the data input, the interpretation and diffusion of results. However, a pitfall to collaboration with relevant stakeholders could be the independency of the researcher. Researchers need to be aware that the more intense the collaboration, the greater the conflict-of-interest threat.

Additionally, in order to increase the uptake of cost-effectiveness evidence from prevention interventions by health professionals and policy makers, health economic researchers need to educate stakeholders on the relevance of cost-effectiveness analysis to policy and practice, on how such analyses are performed, what uncertainties can be involved and how the results should be interpreted. This could be effectuatued for example by organising health economic information sessions for health professionals when participating in a joint project or by organising seminars targeted at public health policy makers as well as lunch meetings with health professionals.

3.4.2. Recommendations for health professionals

Study results from cost-effectiveness analyses are interesting for health professionals as well, mainly in developing and implementing interventions. While developing a prevention intervention, health professionals should keep in mind the factors with the highest impact on the cost-effectiveness, shown from studies such as those included in this PhD research. More specifically, health professionals should think about the potential harms of the intervention and include modules in the intervention to be able to capture the effect of such potential harms on the participant's quality of life and participation/compliance. This could be explored for example in a questionnaire to the participants. Additionally, collecting information on the participant's quality of life in intervention trials could be useful to estimate the value of intermediate outcomes to the participants. Other common factors highly influencing the cost-effectiveness result in the evaluated studies, which health professionals could take into account were the effectiveness of the intervention (as well as the duration of the effect) and in some cases the cost of the intervention. Therefore, we recommend health professionals to conduct more longitudinal research with a follow-up in the long term. Besides, we advise health professionals to keep the intervention cost as low as possible, while maintaining the effectiveness of the intervention. Input from published cost-effectiveness studies can provide tips and tricks on how to achieve this. Besides, it was shown that up to now equity issues are seldom included in cost-effectiveness analyses. In order to improve the incorporation of equity issues, health professionals could take into account heterogeneity by conducting subgroup analyses while evaluating the intervention effect.

3.4.3. Recommendations for policy makers

Firstly, we want to stress that policy makers should keep in mind that even those interventions that do not result in total cost-savings, can still be desirable dependent on the balance between health effects and extra total costs which is assessed against the willingness-to-pay threshold. Additionally, policy makers should facilitate the use of cost-effectiveness as a means of identifying the most valuable preventive services by funding research producing cost-effectiveness evidence, by assessing the

transferability of international cost-effectiveness studies, by having health economic training in order to better understand cost-effectiveness analyses, by disseminating results of cost-effectiveness studies to relevant stakeholders and by using such evidence as information when making a policy decision (Goodell et al., 2009). Besides, policy could support health economic research not only by funding research, but also by investing in improving and integrating databases and by facilitating access to those data for research aims. Furthermore policy makers have to take into account that cost-effectiveness analyses of public health intervention simulating costs and health effects over the long term are generally based on short-term data and therefore the calculations resulting from the modelling are predictions, which include uncertainty. Whether a model is sufficiently valid or accurate for a particular application must be determined by those who use its results (Eddy et al., 2012). According to Threlfall et al. (2015), the important question is not whether it is scientific to make decisions based on predictions, but how much uncertainty the policy maker is willing to accept. It is assumed that in case of prevention within public health, more uncertainty is allowed, as long term evidence is more difficult to assess. In practice, policy makers cannot wait for independent external validation data before a decision is made. However, if data becomes available the model predictions should be tested against this data. Finally, policy makers should be more transparent in the decision making criteria and the relative importance of the different criteria in each decision.

1. EQ-5D questionnaire

Zet bij iedere groep in de lijst hieronder een kruisje in het hokje achter de zin die het best past bij uw eigen gezondheidstoestand vandaag. **Met "ik"wordt de patiënt bedoeld!**

MOBILITEIT
Ik heb geen problemen met rondwandelen ❑
Ik heb een beetje problemen met rondwandelen ❑
Ik heb matige problemen met rondwandelen ❑
Ik heb ernstige problemen met rondwandelen ❑
Ik ben niet in staat om rond te wandelen ❑

ZELFZORG
Ik heb geen problemen met mijzelf te wassen of aan te kleden ❑
Ik heb een beetje problemen met mijzelf te wassen of aan te kleden ❑
Ik heb matige problemen met mijzelf te wassen of aan te kleden ❑
Ik heb ernstige problemen met mijzelf te wassen of aan te kleden ❑
Ik ben niet in staat mijzelf te wassen of aan te kleden ❑

DAGELIJKSE ACTIVITEITEN *(bijv. werk, studie, huishouden, gezins- en vrijetijdsactiviteiten)*
Ik heb geen problemen met mijn dagelijkse activiteiten ❑
Ik heb een beetje problemen met mijn dagelijkse activiteiten ❑
Ik heb matige problemen met mijn dagelijkse activiteiten ❑
Ik heb ernstige problemen met mijn dagelijkse activiteiten ❑
Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren ❑

PIJN/ONGEMAK
Ik heb geen pijn of ongemak ❑
Ik heb een beetje pijn of ongemak ❑
Ik heb matige pijn of ongemak ❑
Ik heb ernstige pijn of ongemak ❑
Ik heb extreme pijn of ongemak ❑

ANGST/DEPRESSIE
Ik ben niet angstig of depressief ❑
Ik ben een beetje angstig of depressief ❑
Ik ben matig angstig of depressief ❑
Ik ben erg angstig of depressief ❑
Ik ben extreem angstig of depressief ❑

Via deze meetschaal willen we weten hoe goed of slecht uw algemene gezondheidstoestand VANDAAG is. Deze meetschaal (te vergelijken met een thermometer) is genummerd van 0 tot 100.

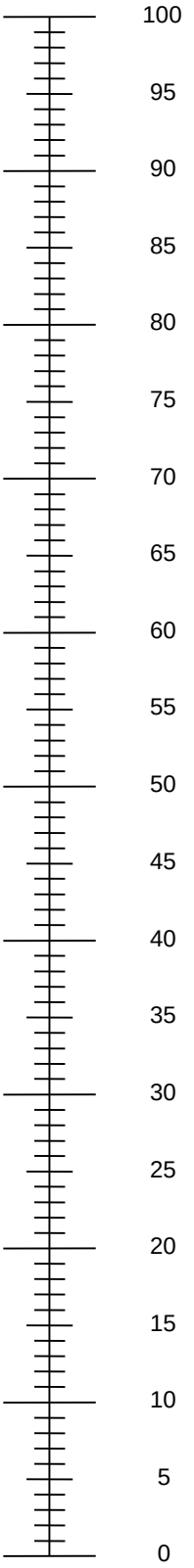
100 staat voor de beste gezondheid die u zich kunt voorstellen.
0 staat voor de slechtste gezondheid die u zich kunt voorstellen.

Plaats een X op de meetschaal om aan te geven hoe uw gezondheid VANDAAG is.

Noteer nu het getal dat u aangeduid hebt op de meetschaal in het onderstaande vakje.

UW GEZONDHEID VANDAAG = ☐

De beste gezondheid die u zich kunt voorstellen



De slechtste gezondheid die u zich kunt voorstellen

2. Questionnaire used in the studies on skin cancer prevention, in order to estimate the costs, utilities and productivity loss:

Studie naar medische consumptie, levenskwaliteit en werksituatie van personen met huidkanker

A) Inleiding

Beste patiënt, dank om mee te werken aan deze studie. U bent geselecteerd om deze vragenlijst in te vullen via uw behandelende arts. Graag willen wij een aantal vragen stellen over uw levenskwaliteit en nagaan hoe vaak u gebruik gemaakt hebt van medische zorgen tijdens de afgelopen 6 maanden en hoe uw woon-werk-situatie eruit ziet.
De studie wordt uitgevoerd in het kader van een doctoraat aan de universiteit van Gent, in samenwerking met de dienst Dermatologie van het UZ Gent. U mag deze vragenlijst zelf invullen; als dit niet kan, mag uw arts, een verpleegkundige, een verzorger of een familielid die nauw bij de uw zorg betrokken is, helpen om de vragenlijst mee in te vullen.

B) Algemene vragen

1. Op welke datum vult u deze vragenlijst in?

_____ _____ _____

dag maand jaar

2. Wat is uw leeftijd?:
……jaar

3. Wat is uw geslacht? (kruis aan):
❑Man ❑Vrouw

4. Wat is uw hoogste diploma?
❑ Lagere school ❑Middelbaar onderwijs ❑ Hoger onderwijs ❑ Universitair diploma

5. Via welke arts kreeg u deze vragenlijst mee (naam)?

……..

6. Welke van de volgende diagnose werd bij u vastgesteld (kruis aan)
(BCC: basocellulair carcinooom; SCC: spinocellulair carcinoom)

❑ BCC <1cm
❑ BCC 1-2cm
❑ BCC >2cm
❑ BCC, agressieve histologie
❑ Multipele BCC
❑ SCCstadium 0 (Bowen)
❑ Spinocellulair carcinoom stadium I of II
❑ SCC stadium III (regionale uitzaaiing)
❑ SCC stadium IV (gemetastaseerde uitzaaiing)
❑ Melanoom stadium 0 (in situ)
❑ Melanoom stadium I (T1-2a, N0, M0)
❑ Melanoom stadium II (T2b-4b, N0, M0)
❑ Melanoom stadium III(T1-4, N1-3, M0)
❑ Melanoom stadium IV(T1-4, N, M1)

7. Op welke locatie werd deze diagnose vastgesteld?
❑ Scalp
❑ Wangen
❑ Oren
❑ Onderarmen
❑ Onderbenen
❑ Andere: _____
❑ Voorhoofd
❑ Neus
❑ Thorax
❑ Handen
❑ Voeten

8. Op welke datum werd deze diagnose gesteld? (m.a.w de datum van de uitslag van de biopsie)

_____ _____ _____

dag maand jaar

In het verdere verloop van de vragenlijst zullen we naar deze diagnose verwijzen als ‘uw huidaandoening’

C) Levenskwaliteit

Zet bij iedere groep in de lijst hieronder een kruisje in het hokje achter de zin die het best past bij uw eigen gezondheidstoestand vandaag. **Met “ik”wordt de patiënt bedoeld!**

MOBILITEIT

Ik heb geen problemen met rondwandelen	❑
Ik heb een beetje problemen met rondwandelen	❑
Ik heb matige problemen met rondwandelen	❑
Ik heb ernstige problemen met rondwandelen	❑
Ik ben niet in staat om rond te wandelen	❑

ZELFZORG

Ik heb geen problemen met mijzelf te wassen of aan te kleden	❑
Ik heb een beetje problemen met mijzelf te wassen of aan te kleden	❑
Ik heb matige problemen met mijzelf te wassen of aan te kleden	❑
Ik heb ernstige problemen met mijzelf te wassen of aan te kleden	❑
Ik ben niet in staat mijzelf te wassen of aan te kleden	❑

DAGELIJKSE ACTIVITEITEN *(bijv. werk, studie, huishouden, gezins- en vrijetijdsactiviteiten)*

Ik heb geen problemen met mijn dagelijkse activiteiten	❑
Ik heb een beetje problemen met mijn dagelijkse activiteiten	❑
Ik heb matige problemen met mijn dagelijkse activiteiten	❑
Ik heb ernstige problemen met mijn dagelijkse activiteiten	❑
Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren	❑

PIJN/ONGEMAK

Ik heb geen pijn of ongemak	❑
Ik heb een beetje pijn of ongemak	❑
Ik heb matige pijn of ongemak	❑
Ik heb ernstige pijn of ongemak	❑
Ik heb extreme pijn of ongemak	❑

ANGST/DEPRESSIE

Ik ben niet angstig of depressief	❑
Ik ben een beetje angstig of depressief	❑
Ik ben matig angstig of depressief	❑
Ik ben erg angstig of depressief	❑
Ik ben extreem angstig of depressief	❑

Via deze meetschaal willen we weten hoe goed of slecht uw algemene gezondheidstoestand VANDAAG is. Deze meetschaal (te vergelijken met een thermometer) is genummerd van 0 tot 100.

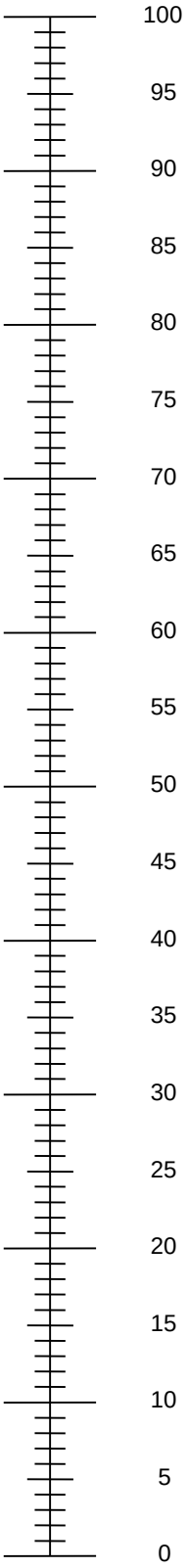
100 staat voor de beste gezondheid die u zich kunt voorstellen.
0 staat voor de slechtste gezondheid die u zich kunt voorstellen.

Plaats een X op de meetschaal om aan te geven hoe uw gezondheid VANDAAG is.

Noteer nu het getal dat u aangeduid hebt op de meetschaal in het onderstaande vakje.

UW GEZONDHEID VANDAAG = ☐

De beste gezondheid die u zich kunt voorstellen



De slechtste gezondheid die u zich kunt voorstellen

D) Huidig gebruik van medische verzorging

In de volgende vragen wordt met "u" de patiënt bedoeld, ongeacht wie deze vragen invult.

I. Hospitalisatie

1. Bent u naar de dagkliniek geweest de afgelopen 6 maanden, in verband met uw huidaandoening?

❑ Neen
❑ Ja Hoeveel dagen in totaal? ……..

2. Heeft u in een ziekenhuis verbleven de afgelopen 6 maanden, in verband met uw huidaandoening?

❑ Neen
❑ Ja Hoeveel dagen in totaal? .....

**dagkliniek: u wordt opgenomen maar mag diezelfde dag nog naar huis*

3. Indien 'Ja' op vraag 1 en/of vraag 2, gelieve in te vullen hoeveel keer u welk vervoersmiddel hebt gebruikt, hoeveel van uw tijd dit transport in beslag nam, hoeveel kilometer de rit was (indien met auto) en de kostprijs van het ticket (indien openbaar vervoer)
(bv. U bent drie keer in het ziekenhuis of dagkliniek geweest, waarvan 2 keer met de auto en 1 keer met openbaar vervoer + een stukje te voet → dan vult u 2 keer in in het vakje na auto, 1 keer in het vakje na openbaar vervoer en 1 keer in het vakje naast te voet)

Vervoersmiddel	Aantal keer	Gespendeerde tijd aan dit transport per keer (heen en terug)	Aantal km per keer (heen en terug)	Kostprijs ticket per keer (heen en terug)
Auto (als chauffeur of als passagier)	…….. keer als chauffeur	……u …..min	..……km	
		……u …..min	..……km	
	…….. keer als passagier	……u …..min	……km	
Openbaar vervoer	…….. keer	…….u …..min		€……..
Te voet of met de fiets	…….. keer	..…u …..min		

II. Consultaties

Toelichting
Wij willen graag weten met welke dokters of zorgverleners u in de afgelopen 6 maanden een afspraak/consultatie had in verband met uw huidaandoening. Het gaat om afspraken voor uzelf.

Welke afspraken tellen mee?
* Controles in verband met uw huidaandoening
* Afspraken/consultaties omdat u een lichamelijke of psychische klacht had in verband met uw huidaandoening
* Afspraken/bezoeken waarbij de dokter bij u thuis kwam in verband met uw huidaandoening
* Afspraken voor een (kleine) ingreep in verband met uw huidaandoening

Wat telt niet mee?
* Afspraken voor een ander, bijvoorbeeld voor uw kind
* Telefoontjes om een afspraak te maken

Weet u niet precies hoeveel consultaties het waren? Schrijf dan op hoeveel het er ongeveer waren

		Hoeveel keer had u een consultatie? (de afgelopen 6 maanden)	Waar had u deze consultatie(s) de afgelopen 6 maanden?				
			Consultatie in spreek-kamer van de arts	Consultatie thuisbezoek	Consultatie tijdens een hospitalisatie	Consultatie in het ziekenhuis (zonder gehospitaliseerd te zijn)	Consultatie spoedgevallen
❑	**Dermatoloog**						
❑	**Huisarts**						
❑	**Oncoloog**						
❑	**Radioloog**						
❑	**Plastisch chirurg**						
❑	**Andere specialist specificeer:** ……						

1. **Indien u minstens 1 consultatie had de laatste 6 maanden, gelieve in onderstaande tabel in te vullen hoeveel keer u welk vervoersmiddel hebt gebruikt om naar de consultatie te gaan, hoeveel van uw tijd dit transport in beslag nam, hoeveel kilometer de rit was (indien met auto) en de kostprijs van het ticket (indien openbaar vervoer)**
   (bv. U hebt drie keer een consultatie gehad, waarvan u er 2 keer met de auto heen ging en 1 keer met openbaar vervoer + een stukje te voet → dan vult u 2 keer in in het vakje na auto, 1 keer in het vakje na openbaar vervoer en 1 keer in het vakje naast te voet)

Vervoersmiddel	Aantal keer	Gespendeerde tijd aan dit transport per keer (heen en terug)	Aantal km per keer (heen en terug)	Kostprijs ticket per keer (heen en terug)
Auto (als chauffeur of als passagier)	…….. keer als chauffeur	……u …..min	..……km	
		……u …..min	..……km	
	…….. keer als passagier	……u …..min	……km	
Openbaar vervoer	…….. keer	…….u …..min		€……..
Te voet of met de fiets	…….. keer	……u …..min		

III. Onderzoeken & Behandeling

Heeft u de voorbije 6 maanden testen, chirurgische ingrepen, onderzoeken of andere niet-medicamenteuze interventies (bv. bloedtransfusie) ondergaan in functie van diagnose en behandeling van uw huidaandoening?

1) ONDERZOEKEN TER DIAGNOSE EN/OF OPVOLGING (kruis aan (meerdere opties mogelijk)+ geef weer hoeveel keer)

- ❑ Dermoscopie. Aantal keer: …….
- ❑ Biopsie. Aantal keer:……..
- ❑ Echografie lymfeklieren. Aantal keer:……
- ❑ Echografie buik. Aantal keer:……
- ❑ CT-scan longen. Aantal keer:…….
- ❑ CT-scan buik. Aantal keer:……..
- ❑ CT-scan lever. Aantal keer:…….
- ❑ CT-scan hersenen. Aantal keer:……..
- ❑ MRI-scan hersenen. Aantal keer:……..
- ❑ PET-scan. Aantal keer:……..
- ❑ RX Thorax. Aantal keer:……..
- ❑ Andere, specificeer aub: ……
- ❑ Geen

2) BEHANDELING (kruis aan (meerdere opties mogelijk) + geef weer hoeveel keer)

- ❑ Chirurgisch wegnemen van een huidplekje . Aantal keer:……..
- ❑ Curettage (wegschrapen) al dan niet in combinatie met dichtschroeien. Aantal keer: ……
- ❑ Bevriezing (cryotherapie). Aantal keer:……..
- ❑ Laser. Aantal keer:……..
- ❑ Fotodynamische therapie (behandeling met bijtende crème en lamp). Aantal keer:……
- ❑ Behandeling met een bijtende crème (bijvoorbeeld Aldara, Picato, Efudix) ➔ Is een medicijn, dus gelieve dit ook te vermelden bij de vraag naar gebruik van medicatie. Aantal keer:……..
- ❑ Bestraling (radiotherapie). Aantal keer:……..
- ❑ Chirurgisch verwijderen lymfeklier (enkel de sentinel/wachtpost-klier(en)). Aantal keer:……
- ❑ Chirurgisch verwijderen lymfeklieren (gehele klierstation) . Aantal keer:……..
- ❑ Immunotherapie (behandeling met medicijnen die de eigen weerstand tegen kankercellen versterken, bijvoorbeeld interferon, interleukine) ➔ Is een medicijn, dus gelieve dit ook te vermelden bij de vraag naar gebruik van medicatie. Aantal keer:……..
- ❑ Algemene chemotherapie (bij gemetastaseerd melanoom, SCC) ➔ Is een medicijn, dus gelieve dit ook te vermelden bij de vraag naar gebruik van medicatie. Aantal keer:……..
- ❑ Andere, specificeer aub: ……

IV. Medicatie

Gelieve op deze pagina alle geneesmiddelen te noteren die u genomen heeft/neemt gedurende de voorbije 6 maanden, voor de verzorging en behandeling van uw huidaandoening en de klachten die ermee gepaard gaan, en voor de verzorging van de eventuele nevenwerkingen van de behandeling. Zalf/crème dient hier ook vermeld te worden.

GENOMEN GENEESMIDDEL VOOR UW HUIDAANDOENING (NIET VOOR ANDERE GEZONDHEIDSKLACHT!) Naam van het product, dosis (indien zalf dan niet in te vullen) en de vorm (zalf, pil, capsule, siroop, injectie)			**AANTAL** Hoeveel keer per dag?	**PERIODE** Hoeveel dagen heeft u dit product de laatste 6 maand gebruikt? *(max = 180)*
Naam product	**Dosis die u neemt** **per keer**	**Vorm van het product** zalf, pil, capsule, siroop, injectie)		
Voorbeeld: Nurofen	*Voorbeeld: 400 mg*	*Voorbeeld: pil*	*Voorbeeld: 3*	*Voorbeeld: 14*

E) Werk-situatie

1. Kruis aan wat uw werksituatie was vóór diagnose van uw huidaandoening (meerdere mogelijk):

❑ Ik was gepensioneerd
❑ Ik was huisvrouw/huisman
❑ Ik werkte voltijds
❑ Ik werkte deeltijds. Aantal uren per week: …….
❑ Ik was in ziekteverlof
❑ Andere: ……

2. Is uw werksituatie veranderd door uw huidaandoening?

❑ Neen
❑ Ja

Indien JA op vraag 2: Kruis aan wat uw huidige werksituatie is. Indien Neen op vraag 2, ga dan verder naar vraag 3.

❑ Ik ben vervroegd op pensioen gegaan door mijn huidaandoening
❑ Ik ben ontslagen of heb ontslag genomen (door mijn huidaandoening)
❑ Ik ben in ziekteverlof (door mijn huidaandoening)
❑ Ik ben huisvrouw/huisman (door mijn huidaandoening)
❑ Ik werk deeltijds (door mijn huidaandoening). Aantal uren per week: _____

3. Bent u in de afgelopen 6 maanden afwezig geweest van uw werk omwille van de huidaandoening?

❑ Neen
❑ Ja, ik ben ….. werkdagen afwezig geweest
❑ Ja, ik ben reeds ….. werkdagen afwezig, en ben het nog steeds

4. **Heeft u, door uw huidaandoening, extra, betaalde huishoudhulp nodig gehad de afgelopen 6 maanden?**

Bijvoorbeeld thuiszorg, hulp voor het poetsen of boodschappen doen
! Indien u bijvoorbeeld een poetsvrouw heeft, maar niet omwille van uw huidletsel, gelieve dan 'neen' aan te kruisen.

❑ Neen
❑ Ja Aantal weken: _____
Aantal uur per week: _____

Dit was de laatste vraag. Hartelijk dank voor uw medewerking aan deze studie!
Indien u vragen hebt, dan mag u contact opnemen met
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Summary

Chronic non-communicable diseases (CNCDs) are the largest contributors to the population health burden and it is expected that their incidence will keep on rising in the next decades, mainly due to ageing of the population and changing health behaviours. Not only population health is affected by these CNCDs, but also the health budget. It is estimated that 70% to 80% of the health budget is spent on the treatment of CNCDs. Health care costs as well as costs due to productivity loss are putting the public budget under huge pressure. As such, the concern has been raised on the financial sustainability of the health care system. The World Health Organization recommends to promote public health interventions that prevent and control CNCDs in order to lessen their global health and economic impact. Governments should invest in prevention interventions that offer good value for money, by considering cost-effectiveness evidence in the decision-making process. However, the use of cost-effectiveness evidence, especially of public health prevention interventions, has been estimated to be limited. This is mainly due to the availability, quality and transparency of such evidence, the clarity of its presentation and the extent to which policy makers understand such analyses.

Therefore, the first aim of this PhD-thesis was to assess the cost-effectiveness of 8 public health interventions in the continuum of CNCD prevention, that hold some promise to reduce the health burden at a reasonable cost or even at a lower total cost. Universal prevention interventions included in this PhD research comprised the prevention of obesity in pre-schoolers, as well as a sensitisation campaign and a total ban on sunbed use to prevent skin cancer. The evaluation of interventions categorised as selective prevention consisted of a biennial mammography screening program for the early detection of breast cancer, a biennial faecal immunological test for the early detection of colorectal cancer, a total-body examination and a lesion-directed screening for the early detection of skin cancer. Finally, the indicated prevention intervention was a suicide helpline for the prevention of suicide. All analysed interventions showed potential for increasing population health while controlling the health care budget. These interventions were found to result in incremental cost-effectiveness ratios being below the assumed threshold of €35,000/QALY gained, which means that public investment in these interventions would offer good value for money. However, the strength of the evidence was stronger in some studies than in others, dependent on the inherent uncertainties that should be taken into account while interpreting these cost-effectiveness results. It needs to be stated that cost-effectiveness analyses include inherent uncertainties concerning the model structure (structural uncertainty), availability of data (parameter uncertainty) and the methodological choices (methodological uncertainty), some being specific to the field of public health prevention interventions, such as providing indirect evidence, the choice of time horizon, duration of the intervention-effect, the use of QALYs as outcome measure, and some being related to cost-effectiveness analysis in general, such as the lack of data, choice and valuation of costs to include, harms of the intervention, etcetera.

Our second aim was to inform researchers as well as policy makers and other stakeholders on these uncertainties and their impact on the interpretation of cost-effectiveness results. This was performed by reporting and reflecting on the main uncertainties that we encountered in the included cost-effectiveness

analyses. By interpreting the study results in light of these uncertainties, it was shown that the results of the study on prevention of pre-schooler obesity should be interpreted with caution as there is still a lot of uncertainty on the duration of the intervention effect and the extrapolation of the effect in pre-schoolers to adulthood, both influencing the cost-effectiveness result. The universal prevention interventions to prevent skin cancer were hypothetical interventions. Although the results were promising (both were predicted to be dominant) and seemed quite robust, it is advisable to first conduct further research on what the effectiveness of such measures is or may be in a Belgian context. As it es expected that the incidence of skin cancer and the cost of treating skin cancer will increase in the future, it was shown that prevention of skin cancer would become more cost-effective. The screening programs on breast- and colorectal cancer are already implemented in Flanders. As such, screening-related data was obtained from these existing programs. Both programs were found to be cost-effective and therefore advised to be continued. However, further research is needed on the quality of life related to these cancers and to a false-positive result as both influence the cost-effectiveness of screening. Also, more information on the long-term impact of screening on mortality and the incidence of new tumours (in the further stages) is desirable, in order to verify whether the model predictions are correct. Furthermore, as the screening techniques as wel as treatment therapies are continuously evolving, frequent evaluation is necessary. A one-time skin cancer screening was shown to be a cost-effective strategy, especially in women; a total body examination showed a slightly better result on cost-effectivenss than the lesion-directed screening (which was only due to the participation rate). However, more information on the natural progression of skin cancer as well as a systematic registration of NMSC lesions in Belgium would improve cost-effectiveness research, as the sensitivity analysis showed that screening for basal cel carcinoma might not offer good value for money in case of a high prevalence. By means of this study we were able to make recommendations for skin cancer prevention in the future, though more research on skin cancer screening to confirm our results (and the most efficient target group and screening interval) is desirable. The largest uncertainty in the study of the suicide helpline was the lack of information on the effectiveness of the suicide helpline in Flanders and the lack of information about the cost of a (fatal) suicide attempt. On the other hand, based on the results of the sensitivity analysis, we can say that the Flemish suicide helpline is a cost-effective, and even dominant strategy. However, if we want more clarity on the magnitude of the cost savings, it is necessary first to have more information on the effectiveness of the Flemish suicide helpline and the cost of a (fatal) suicide attempt in Flanders/Belgium. From our studies, we concluded that uncertainty in cost-effectiveness studies offers interesting information, in addition to the mean result, that should be reported transparently in order for the results to be interpreted in light of these uncertainties. In this way, we stressed the importance of scenario- and sensitivity analyses and validation efforts.

By our research we informed several stakeholders who may be performing, funding, participating in, or making use of economic evaluations and formulated some recommendations for future practice and policy. *Researchers* performing cost-effectiveness analyses need to be aware of the included uncertainties and explore the impact on the result. Mean (base case) cost-effectiveness results provide relevant information, but results from sensitivity analyses and model validation exercises are even more

informing. Furthermore, in order to enhance the quality of the cost-effectiveness evidence researchers should cooperate with relevant stakeholders, before, during or after performing the analysis. This could be achieved by selecting a stakeholder group, representing clinical and health economic experts as well as data registries and policy makers where possible. Also, to increase recognisability and uptake of of cost-effectiveness evidence from prevention interventions by health professionals and policy makers, health economic researchers need to educate stakeholders on the relevance of cost-effectiveness analysis to policy and practice, on how such analyses are performed, what uncertainties can be involved and how the results should be interpreted. This could be effectuatued for example by organising health economic information sessions for health professionals when participating in a joint project or by organising seminars targeted at public health policy makers as well as lunch meetings with health professionals. Study results from cost-effectiveness analyses are interesting for *health professionals* as well, mainly in developing and implementing interventions. While developing a prevention intervention, health professionals should keep in mind the factors with the highest impact on the cost-effectiveness, shown from studies such as those included in this PhD research. More specifically, health professionals should think about the potential harms of the intervention and include modules in the intervention trial to be able to capture the effect of such potential harms on the participant's quality of life and participation/compliance. Besides, collecting information on the participant's quality of life is also recommended to increase our knowledge on the value of intermediate outcomes to the participants. Other common factors highly influencing the cost-effectiveness result in the evaluated studies, which health professionals could take into account, were the effectiveness of the intervention (as well as the duration of the effect) and in some cases the cost of the intervention. More longitudinal research with a follow-up in the long term is advised. Besides, it was shown that up to now equity issues are seldom included in cost-effectiveness analyses. In order to improve the incorporation of equity issues, health professionals could take into account heterogeneity by conducting subgroup analyses while evaluating the intervention effect. *Policy makers* should facilitate the use of cost-effectiveness evidence as a means of identifying the most valuable preventive services by funding research producing such evidence, by assessing the transferability of international cost-effectiveness studies, by having health economic training in order to better understand cost-effectiveness analyses, by disseminating results of cost-effectiveness studies to relevant stakeholders and by using such evidence as information when making a policy decision. Besides, policy could support health economic research not only by funding research projects, but also by investing in improving and integrating databases and by facilitating access to those data for research aims. Furthermore, policy makers have to be aware that cost-effectiveness analyses include uncertainty. Whether a model is sufficiently valid or accurate for a particular application must be determined by those who use its results. The important question is not whether it is scientific to make decisions based on predictions, but how much uncertainty the policy maker is willing to accept. It is assumed that in case of prevention within public health, more uncertainty is allowed, as long term evidence is more difficult to assess. Finally, policy makers should be more transparent in the decision making criteria and the relative importance of the different criteria in each decision.

Samenvatting

Chronische niet-overdraagbare ziektes (CNOZs) zijn de grootste oorzaken van ziekte en sterfte op populatieniveau. Er wordt verwacht dat de incidentie van deze ziektes zal blijven stijgen in de komende decennia, voornamelijk als gevolg van de vergrijzing van de bevolking, maar ook door veranderingen in de levensstijl van de bevolking. Niet alleen de volksgezondheid wordt beïnvloed door deze CNCDs, maar ook het budget van de gezondheidszorg. Er wordt naar schatting 70% tot 80% van het gezondheidsbudget gespendeerd aan de behandeling van CNOZs. De kosten voor de gezondheidszorg mede als de kosten omwille van productiviteitsverlies zetten de overheidsbegroting onder enorme druk. Als gevolg van deze trend wordt de financiële houdbaarheid van de gezondheidszorg in vraag gesteld. De Wereldgezondheidsorganisatie adviseert om in te zetten op preventieve interventies die kosteneffectief zijn, i.e. waarde voor hun geld bieden, om de impact van CNOZs op de volksgezondheid en het gezondheidsbudget te beheersen. Kosteneffectiviteitsanalyses informeren beleidsmakers over de verhouding tussen de kost en gezondheidswinst van interventies. Echter, het gebruik van informatie over de kosteneffectiviteit van interventies in besluitvorming, in het bijzonder van preventieve interventies ter bevordering van de volksgezondheid, wordt ingeschat als zijnde beperkt. Dit is voornamelijk te wijten aan de beschikbaarheid van dergelijke informatie, de kwaliteit en transparantie ervan en de mate waarin de beleidsmakers dergelijke analyses begrijpen.

Daarom was een eerste doelstelling van dit proefschrift om de kosteneffectiviteit te evalueren van acht interventies in het continuüm van CNOZ-preventie, die de gezondheid trachten te bevorderen door te focussen op de belangrijkste CNOZs. Interventies die in dit proefschrift in de categorie van universele preventie werden gecategoriseerd omvatten de preventie van overgewicht en obesitas bij kleuters, evenals een sensibiliseringscampagne en een totaal verbod op zonnebankgebruik ter preventie van huidkanker. Interventies binnen de selectieve preventie bestonden uit een tweejaarlijkse mammografiescreening voor de vroegtijdige opsporing van borstkanker, een tweejaarlijkse fecale immunologische test voor de vroege opsporing van dikkedarmkanker, een onderzoek van het totale lichaam en een vlekjesscreening voor de vroegtijdige detectie van huidkanker. Tenslotte bevatte de categorie van geïndiceerde preventie de evaluatie van een hulplijn ter preventie van zelfmoord. Alle interventies toonden potentieel in het verbeteren van de volksgezondheid en het controleren van de uitgaven aan gezondheidszorg. Deze interventies hadden een incrementele kosteneffectiviteitsratio die onder de veronderstelde drempelwaarde van €35.000 per gewonnen levensjaar lag, wat betekent dat overheidsinvestering in deze interventies extra gezonde levensjaren zou bieden tegenover een matige kostprijs of soms zelfs kostenbesparingen. Echter, de sterkte van het resultaat verschilde van studie tot studie, afhankelijk van de inherente onzekerheden in de analyses waarmee rekening moet gehouden worden bij het interpreteren van de resultaten. Het moet worden vermeld dat kosteneffectiviteitsanalyses onzekerheden bevatten met betrekking tot de structuur van het model (structurele onzekerheid), beschikbaarheid van invoergegevens (parameter onzekerheid) en de methodologische keuzes (methodologische onzekerheid). Sommige van deze onzekerheden gelden specifiek voor kosteneffectiviteitsanalyses van preventie interventies, zoals het aanleveren van indirect bewijs, de keuze van de tijdshorizon, de duur van de interventie-effect, het gebruik van QALYs als

uitkomstmaat. Andere onzekerheden gelden voor kosteneffectiviteitsanalyses in het algemeen, zoals het gebrek aan gegevens, de keuze en de waardering van kosten, includeren van nadelen van de interventie, etcetera.

Het tweede doel van dit proefschrift was om zowel onderzoekers als beleidsmakers en andere belanghebbenden te informeren over deze onzekerheden en hun invloed op de interpretatie van kosteneffectiviteit resultaten. Onzekerheden die werden vastgesteld tijdens het uitvoeren van de analyses werden gerapporteerd en de invloed ervan op het resultaat van de analyse werd onderzocht. Zo werd aangetoond dat de resultaten van de studie omtrent preventie van obesitas bij kleuters met enige voorzichtigheid geïnterpreteerd moeten worden, aangezien er nog veel onzekerheid is over de duur van het interventie-effect en de extrapolatie van het effect in kleuters naar volwassen leeftijd, dewelke beide de kosteneffectiviteit sterk beïnvloeden. De universele interventies ter preventie van huidkanker waren hypothetische interventies. Hoewel de resultaten van de analyse veelbelovend zijn (beide werden voorspeld dominant te zijn op lange termijn) en vrij robust bleken, is het aanbevolen om eerst verder onderzoek te voeren naar de effectiviteit van dergelijke maatregelen in een Belgische context. Aangezien verwacht wordt dat de incidentie van huidkanker en de kost om het te behandelen zal stijgen in de toekomst, werden deze scenario's geanalyseerd en werd aangetoond dat deze trends de nood aan dergelijke preventieve interventies verhogen en de kosteneffectiviteit ervan verbeteren. De screening programma's naar borst- en dikkedarmkanker zijn reeds geïmplementeerd in Vlaanderen, waardoor de screening-gerelateerde data van deze bestaande programma's kon verkregen worden. Beide bevolkingsonderzoeken werden geëvalueerd als zijnde kosteneffectief en daardoor aanbevolen om verdergezet te worden. Echter, meer onderzoek is nodig naar de kwaliteit van leven gerelateerd aan deze kankers en aan een vals-positief resultaat op de screeningstest, aangezien beide de kosteneffectiviteit van screening sterk blijken te beïnvloeden. Ook is meer informatie welkom omtrent de langetermijn impact van screening op de mortaliteit en incidentie van nieuwe tumoren (in de verder gevorderde stadia), om de voorspellingen van het model op lange termijn te toetsen. Bovendien is frequente evaluatie van de bevolkingsonderzoeken aangeraden aangezien de screeningstechnieken en behandelingen van deze kankers voortdurend evolueren en de kosteneffctiviteit van screening beïnvloeden. Een éénmalige huidkankerscreening bleek kosteneffectief te zijn, vooral bij vrouwen; een gehele lichaamsinspectie toonde een lichtjes betere kosteneffectiviteit dan een vlekjesscreening (maar dit was enkel te wijten aan de lagere participatiegraad in deze tweede groep). Meer informatie over de natuurlijke progressie van huidkanker evenals een systematische registratie van niet-melanome letsels in België zou onderzoek bevorderen, aangezien de sensitiviteitsanalyse aantoonde dat screening naar basaalcelcarcinoom minder waarde voor z'n geld zou bieden in geval van een hogere prevalentie. Door middel van deze studie konden we aanbevelingen doen over huidkankerscreening in de toekomst, hoewel verder onderzoek nodig is om deze resultaten te bevestigen en om de meest efficiënte doelgroep en screeninginterval te determineren. De grootste onzekerheid in de studie over de zelfmoordlijn wat het gebrek aan informatie over de effectiviteit van de zelfmoordlijn in Vlaanderen en het over de kost van een (fatale) zelfmoordpoging. Anderzijds kunnen we op basis van de resultaten van de sensitiviteitsanalyse met vrij veel zekerheid concluderen dat de Vlaamse zelfmoordlijn kosteneffectief en zelfs dominant blijkt te zijn. Echter, indien we een meer accuraat beeld over de

grootte-orde aan kostenbesparingen willen, is het nuttig om eerst meer informatie te hebben over de effectiviteit van de hulplijn in Vlaanderen en kost van een fatale poging. Door middel van de resultaten van onze studies, kunnen we concluderen dat de onzekerheid in de kosteneffectiviteit studies interessante informatie oplevert die transparant moet worden vermeld, zodat de resultaten in het licht van deze onzekerheden kunnen worden geïnterpreteerd. Op deze manier werd het belang van sensitiviteits- en scenario-analyses belicht, evenals van validatie-oefeningen.

De resultaten die voortvloeien uit dit proefschrift kunnen verschillende belanghebbenden informeren die kosteneffectiviteitsanalyses uitvoeren, financieren of ervan gebruik maken. Verschillende aanbevelingen werden geformuleerd. *Onderzoekers*, die kosteneffectiviteitsanalyses uitvoeren, moeten zich bewust zijn van de onzekerheden in de kosteneffectiviteitsanalyses en de impact ervan op het resultaat evalueren. Het gemiddelde resultaat (basis-scenario) van een kosteneffectiviteitsanalyse biedt relevante informatie, maar de resultaten van de sensitiviteitsanalyses en modelvalidatie zijn nog informatiever. Bovendien, om de kwaliteit van de kosteneffectiviteitsresultaten te verbeteren moeten onderzoekers samenwerken met relevante belanghebben, vóór, tijdens of na het uitvoeren van de analyse. Dit kan worden bewerkstelligd door het selecteren van een groep van belanghebbenden, die zowel klinische als gezondheids(economische) experten maar ook verantwoordelijken van dataregisters vertegenwoordigt. Om ook de herkenbaarheid en het gebruik van de resultaten van kosteneffectiviteitsanalyses door andere onderzoekers, gezondheidswerkers of beleidsmakers te verhogen, moeten onderzoekers belanghebbenden informeren over de relevantie van kosteneffectiviteitsanalyses voor het beleid en de praktijk, over de wijze waarop dergelijke analyses worden uitgevoerd, welke onzekerheden erin kunnen vervat zitten en hoe de resultaten moeten worden geïnterpreteerd in het licht van deze onzekerheden. Dit kan bereikt worden bijvoorbeeld door het organiseren van seminaries voor beleidsmakers evenals lunch-meetings met gezondheidswerkers. De resultaten van dit proefschrift zijn ook informatief voor *gezondheidswerkers,* vooral in het ontwikkelen en implementeren van interventies. Bij de ontwikkeling van een preventieve interventie moeten zorgverleners rekening houden met de factoren die de grootste impact hebben op de kosteneffectiviteit, zoals blijkt uit de studies die zijn opgenomen in dit proefschrift. Meer specifiek raden we gezondheidswerkers aan om ook na te denken over de potentiële nadelige effecten van interventies door modules in de interventietrial te includeren die de impact nagaan op de kwaliteit van leven, maar ook de deelname en naleving van de participant. Bovendien is het verzamelen van informatie omtrent de levenskwaliteit van de participant ook aanbevolen om onze kennis te vergroten omtrent de waarde van intermediaire interventie-effecten voor de participant. Andere gemeenschappelijke parameters met een sterke invloed op het kosteneffectiviteit resultaat, waarmee gezondheidswerkers rekening kunnen houden, zijn de doeltreffendheid van de interventie evenals de duur van het effect en de kosten van de interventie. Meer longitudinaal onderzoek met een follow-up op de lange termijn wordt geadviseerd. Bovendien werd aangetoond dat tot nu toe rechtvaardigheid zelden wordt meegenomen in kosteneffectiviteitsanalyses. Om de integratie van dergelijke informatie te bevorderen, kunnen gezondheidswerkers rekening houden met heterogeniteit door het uitvoeren van subgroepanalyses tijdens de evaluatie van het effect interventie. *Beleidsmakers* moeten het gebruik van informatie over kosteneffectiviteit als een middel voor het identificeren van de meest waardevolle preventieve

interventies bevorderen door het financieren van onderzoek dat dergelijke informatie produceert, door de transfereerbaarheid van internationale kosteneffectiviteitsstudies naar de huidige context te onderzoeken, door training te volgen met het oog op een beter begrip van kosteneffectiviteitsanalyses, door verspreiding van de resultaten van de kosteneffectiviteitsstudies naar relevante belanghebbenden en door de informatie over kosteneffectiviteit mee te nemen in besluitvormingsprocessen. Bovendien kunnen beleidsmakers gezondheidseconomisch onderzoek ondersteunen, niet alleen door financiering van dergelijk onderzoek, maar ook door te investeren in het verbeteren en integreren van databases en door het vergemakkelijken van de toegang tot deze gegevens voor onderzoek. Verder moeten beleidsmakers er rekening mee houden dat kosteneffectiviteitsanalyses onzekerheden includeren. Of een model voldoende valide of accuraat is voor een bepaalde toepassing moet worden bepaald door degenen die de resultaten gebruiken. De vraag is niet of het wetenschappelijk is om beslissingen te nemen op basis van voorspellingen, maar hoeveel onzekerheid de beleidsmaker bereid is te accepteren. Er wordt aangenomen dat bij preventieve interventies die de volksgezondheid bevorderen meer onzekerheid is toegestaan, aangezien het moeilijker is om de effectiviteit van dergelijke interventies op lange termijn te beoordelen. Ten slotte is het van belang dat beleidsmakers meer transparant zijn in de criteria die worden meegenomen in de besluitvorming en het relatieve belang van de verschillende criteria in elke beslissing.

About the author

Lore Pil was born in Leuven on the 3rd of June, 1988. She obtained a MSc degree in Sociology in 2010, and in Health Promotion in 2011, both at Ghent University. In March 2012, she started as a researcher at the same university, in the unit of Health Economics under supervision of prof. Lieven Annemans and prof. Koen Putman. During her PhD-period, she worked on several health economic analyses, with special interest in prevention.

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“Hoe voelt dat nu, zo vier jaar doctoreren?”, vragen mensen me soms. Ik heb er even over moeten nadenken, want er kwamen zoveel gevoelens aan te pas. “Als een rollercoaster”, zeg ik dan. Je kent het wel, je begint eraan zonder goed te weten wat er op je af komt of wat je staat te wachten. Vol goeie moed neem je plaats. Voor je het goed en wel beseft, bereik je in een sneltempo enkele hoogtes en laagtes en net wanneer je denkt dat het even rustiger begint te gaan, word je weer heen en weer geslingerd tussen zalige adrenalinestoten en het ‘ik wil hier uit’-gevoel. En achteraf ben je blij en trots dat je het volbracht hebt. Wel, ik denk dat dit een goede beschrijving is van het avontuur dat ik de voorbije 4,5 jaar heb mogen meemaken. Ik ben trots op het onderzoek dat ik vandaag kan presenteren, maar ook het proces erachter is belangrijk. Dit rollercoaster avontuur heb ik namelijk niet alleen beleefd, vele personen hebben me bijgestaan, zij het van aan de start, van op de zijlijn of bij de finish, zonder wie mijn doctoraat wellicht niet was geweest wat het nu is. Zoals de Dalai Lama het reeds zei: *“The best things in life aren’t things”*; daarom wil ik hier nog even tijd maken om enkele van deze personen in het bijzonder te bedanken.

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