From intermediate to final behavioral endpoints

Modeling cognitions in (cost-)effectiveness analyses in health promotion

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FROM INTERMEDIATE TO FINAL BEHAVIORAL ENDPOINTS

MODELING COGNITIONS IN (COST-)EFFECTIVENESS ANALYSES IN HEALTH PROMOTION

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Contents

1

General introduction

General introduction

Resources in health care are generally limited. Economic evaluations are considered to be an important tool to support decisions on how to allocate the health care budget. In health care systems in developed countries cost-effectiveness analyses (CEAs) have become an accepted method to assess efficiency of health care programs [1,2], as in the field of health psychology and health promotion [3,4]. The cost of health care rises and the awareness of the need to live within health care budgets increases the importance of CEAs [4-6]. Therefore, it is necessary that decision makers are optimally informed about the cost-effectiveness of different treatment options [7].

This introduction provides background information on cost-effectiveness of health promotion, in particular smoking cessation interventions, and why traditional CEAs may not be suited for application in health promotion. Furthermore, it explains how future effects are currently modeled and provides information on the process of behavior change by cognitive antecedents and its implications for CEAs in the area of health promotion. The chapter ends with an overview of the studies performed and are described in the subsequent chapters.

Cost-effectiveness in health promotion

Health promotion is defined as the process of enabling people to increase control over the determinants of health and thereby to improve health [8]. The aim is to have people adopt healthier lifestyles resulting in longer and healthier lives. As smoking is a leading preventable cause of morbidity and mortality, such as chronic obstructive pulmonary disease (COPD) and cardiac diseases, preventing the uptake of smoking and facilitating smoking cessation are among the main goals in health promotion [9].

Extensive evidence exists on the effectiveness of pharmaceutical and behavioral interventions for smoking cessation [10-16]. Also, several studies have addressed its cost-effectiveness for multiple populations [e.g. 17-20]. Feenstra et al. assessed the cost-effectiveness of five Dutch face-to-face smoking cessation interventions. Minimal counseling by general practitioners was found cost-saving compared to current practice, whereas the cost-effectiveness ratios for the remaining interventions were found to be small [19]. For COPD patients it was shown that a combination of pharmacotherapy and behavior counseling is cost-effective compared to usual care [17]. Additionally, among a general population, reimbursement of smoking cessation support would likely result in cost-effective outcomes [18]. In the CEAs described above, as in many others, behavioral interventions are compared to their alternatives with commonly applied CEA methodology, which has originated in the field of medicine and pharmaceutics. However, as was shown in this thesis, due to the unique characteristics of behavioral interventions compared to medical or pharmaceutical treatments, traditional CEA methodology may not be adequate.

Why traditional CEA may not be suited for health promotion

Exploring the cost-effectiveness of a *behavioral* health intervention has some methodological implications compared to other fields. Behavioral interventions encourage individuals to modify their existing behavior and to adopt a healthier behavior. CEAs of behavioral interventions typically focus on objective behavioral data, that is, physical endpoints like weight loss or biochemically validated smoking cessation [21]. In reality, though, behavioral change is a complex process in which several steps towards success are taken, including cognitive changes. As most intervention studies have a relatively short follow-up period of six to 12 months, it is plausible that effects occur *after* the follow-up period. In fact, any progress in cognitive parameters without accomplishing full change in physical endpoints can be considered as a beneficial outcome of the intervention [22]. Not accounting for 'delayed' behavioral change may lead to underestimation of effectiveness of behavioral interventions [23-26]. Similarly, effectiveness can be overestimated due to long-term relapse. This implies that analysts who conduct a CEA of a behavioral intervention should not focus solely on people who successfully changed their behavior, but they also need to account for intermediate or partial behavioral change. Failing to include this in CEA can bias the results [21].

From intermediate to final endpoints

With the purpose of informing decision makers on health effects on the longer term and looking beyond a study's follow-up period, decision analytic models can be applied in economic evaluations. Decision analytic models are common in clinical trials where available trial evidence compares interventions in terms of intermediate endpoints rather than final endpoints. This is frequently the case, for example, in cost-utility analysis when the trials have measured one or a series of clinical endpoints, which are linked to health-related quality of life and hence to utilities and quality-adjusted-life years (QALYs) [2]. An example is the study of Neumann et al. [27], which used Markov modeling to estimate long term quality of life of Alzheimer's disease based on the intermediate endpoint of treatment effect measured by transitions on the Clinical Dementia Rating scale. Also, Kobelt et al. [28] used Markov modeling to assess cost-effectiveness of infliximab in rheumatoid arthritis. They modeled intermediate treatment effects in terms of change in Health Assessment Questionnaire score to long term quality of life.

Also, in the field of health promotion decision analytic models exist to estimate future cost-effectiveness results. For smoking cessation examples are the Tobacco Policy Model [29], the Chronic Disease Model [30] and the COPD model [31]. These models project incidence, prevalence, mortality, progression and healthcare costs of several diseases. Rates for longer term outcomes depend on smoking status, defined as current smoker, non-smoker or ex-smoker. These are examples of *behavioral* intermediate outcomes that precede change in life years and QALYs eventually. However, as described in this thesis, these outcomes may not account for delayed behavioral effects and are not applicable in case information on these endpoints is not available.

In general, the use of intermediate outcomes in CEAs has been criticized in literature. The main counter argument is that a treatment or intervention can improve intermediate outcomes without improving the final outcome [32]. Thus, the validity of intermediate outcomes in CEAs depends on the strength of the evidence linking the intermediate to final outcomes. Moreover, important aspects of the intervention may not be caught in intermediate outcomes. In other words, intermediate outcomes should be caused by the same mechanisms of the intervention as those of the final outcomes. Reliance on solely intermediate outcomes may over- or underestimate final outcomes [1]. A causal relationship between the working mechanisms of the intervention, and intermediate and final endpoints in CEA is therefore a precondition for long-term modeling of these outcomes.

Cognitive intermediate outcomes

For health behavior as final endpoint, cognitive determinants that precede behavior change can be considered as intermediate outcomes. *Cognitive* parameters are the antecedents of actual behavioral change, as described in several behavioral theories in literature. Examples of theories are the Transtheoretical model (TTM) [33], the Theory of Planned Behavior (TPB) [34,35] and Bandura's Social Cognitive Theory (SCT) [36]. A number of cognitive predictors are available from these social-cognitive theories with robust empirical support [37]. For example, self-efficacy expectations (one's confidence to accomplish or to refrain from a certain behavior [36]) has shown consistently to be a valid predictor of a wide range of health behaviors. Also, the stages-of-change algorithm, as part of the TTM, has received ample empirical support [38,39]. Cognitive parameters derived from three theories are applied in the subsequent chapters (i.e. Transtheoretical model, Theory of Planned Behavior, ASE model). These theories are briefly described here.

Transtheoretical Model

The TTM (Figure 1) is the dominant stage model in health psychology and health promotion. It has been widely adopted for numerous health behaviors, but was originally designed to describe addictive behaviors and was based on research of self-initiated quit attempts by smokers [33,40]. A number of qualitatively different, discrete stages are key constructs of this model. It provides an algorithm that distinguishes six stages: 1) pre contemplation (e.g. for smoking cessation, no intention to quit smoking within the next six months); 2) contemplation (e.g. intending to quit smoking within the next six months, but not within the next month); 3) preparation (e.g. intending to quit smoking within the next 30 days); 4) action (e.g. being abstinent for less than six months); 5) maintenance (e.g. being continuously abstinent from smoking for more than six months) [33] and 6) termination (e.g. individuals have zero temptation and they are sure they will not return to their old unhealthy habit as a way of coping [41]). Since termination may not be a practical reality for a majority of people, it has not been given as much emphasis in research. Ten processes of change have been identified for producing progress through these stages, along with decisional balance (pros and cons), self-efficacy, and temptations [41].

The stages-of-change provide the basic organizing principle. People are assumed to move through the stages in order, but they may relapse from action or maintenance to an earlier stage. People may cycle through several stages before achieving long-term behavior change. The decisional balance (pros and cons) are the perceived advantages and disadvantages of changing one's behavior and the processes of change are the covert and overt activities that people engage in to progress through the stages. Self-efficacy, derived from the SCT [36], refers to the confidence that one can carry out the recommended behavior across a range of potentially difficult situations and the related construct of temptation refers to the temptation to engage in the unhealthy behavior across a range of difficult situations. In stage theories, the transitions in stages are assumed to be influenced by the other defined constructs [42].

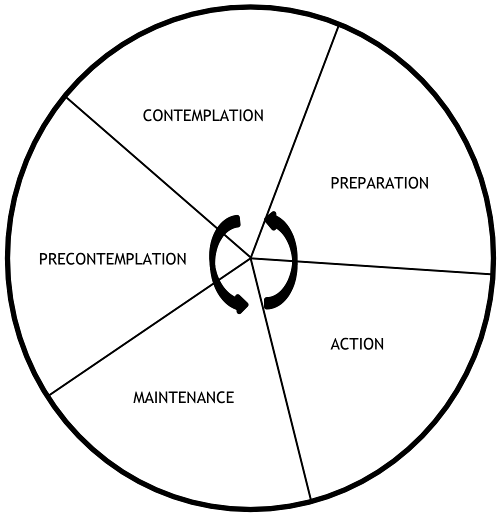

Figure 1. Stages-of-Change algorithm (Transtheoretical Model) [33]

Theory of Planned Behavior

The Theory of Planned Behavior (TPB) (Figure 2) is one of the most influential theories and has been used to predict many health behaviors successfully [34,35]. It proposes that behavior can be predicted by a person's intention to perform that behavior. Behavioral intention represents a person's motivation in the sense of her or his conscious plan, decision or self-instruction to exert effort to perform the target behavior. According to the theory, the behavioral intention is in turn predicted by a positive attitude towards, for example, smoking cessation, a high perceived behavioral control to refrain from smoking, and a high perceived social norm to stop smoking. These proximal variables are on their turn influenced by external or exogenous variables [43]. The TPB is an extension of Ajzen and Fishbein's earlier Theory of Reasoned Action (TRA) [44]. In addition to attitudes and subjective norms (which make the TRA), the TPB adds the concept of perceived behavioral control, which originates from SCT [45]. Although the concepts of perceived behavioral control and self-efficacy are acknowledged to be similar concepts and often measured by the same items [46], there is a distinction. Self-efficacy refers to the conviction that one can successfully execute the behavior required [45], whereas perceived behavioral control refers to the perception of the ease or difficulty of the particular behavior. Furthermore, perceived behavioral control is linked to control beliefs, meaning beliefs about the presence of factors that may facilitate or impede performance of the behavior [34].

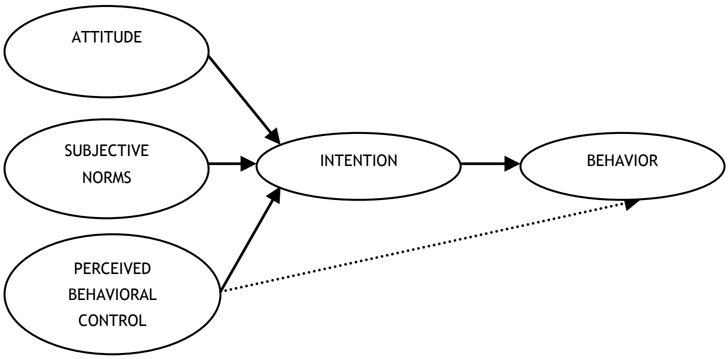

Figure 2. Proximal variables of the Theory of Planned Behavior [34]

ASE model

Closely related to the TPB and derived from the TRA, is the Attitude-Social influence-self-Efficacy (ASE) model [47] (Figure 3). This model is currently known as the I-Change model [48]. The ASE model states that behavior is the result of a person's intentions and abilities. Motivational, proximal factors, such as attitude, social influences and self-efficacy, determine a person's intention. In contrast to the TPB, a decision balance (pros and cons) is described for the attitude construct and self-efficacy is defined as described by Bandura [45]. In addition, the model distinguishes several distal variables, like personality traits or a biological disposition, which affect behavior indirectly through the proximal determinants.

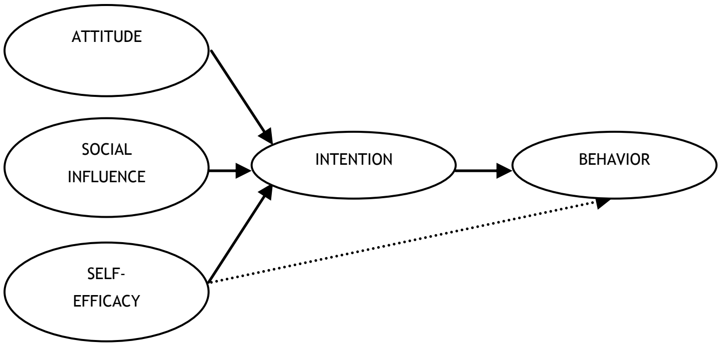

Figure 3. Proximal variables of the Attitude - Social influence – Efficacy Model [49]

Stage-based versus dimensional theories

There is an important feature that distinguishes stage-based models like the TTM, in which individuals are classified into discrete states, from the other dimensional, continuous theories, such as the TPB and ASE model. These models do not distinguish qualitatively different states, but provide a multidimensional change continuum. Therefore, methods to extrapolate the course of psychological variables distinguished by these dimensional theories over the 12 month period to future time points have to be developed.

Prospective research has mostly investigated predictor variables using smoking status at one point in time. However, if the aim is to predict one end point only, but fluctuations of smoking status within individuals at other time points can occur, it may not be valid to solely focus on the data of the end point to be predicted [50]. The complex nature of the human behavior change process makes it difficult to describe via a mathematical or statistical model. Use of a single point measure implies a stability of the outcome variable that is not justified [51]. Even relatively sophisticated methods such as logistic regression analysis generally involve assessment of the outcome at one predetermined follow-up time and assignment of subjects to one of two (or perhaps several) outcome categories. It should be acknowledged that people tend to cycle between smoking and abstinence before reaching a steady state [52]. It is therefore preferable to use models that address a process of multiple quit attempts and relapses and account for cognitive fluctuations over time.

Rationale of the thesis

The relevance of the thesis is defined in its practical applicability to existing interventions. First, it provides a method that can give more insight in long term (cost-) effectiveness of interventions, because it provides a way to look beyond measured (intermediate) endpoints (i.e. behavior) in available data (by predicting them). Second, it can also contribute to the standardization of CEAs, as it will provide the technology to model from varying (cognitive or behavioral) endpoints to a single estimated endpoint. This means that CEA studies that are now incomparable due to different endpoints or time periods, may be adapted to be compared based on the same estimated outcome measure.

CEAs are considered an increasingly important tool in health promotion and psychology. Delayed effects due to post-follow-up behavior change plausibly occur, which may bias results from CEA. Modeling cognitive parameters of behavioral change provide a way to deal with this issue. Parameters like the stages-of-change may serve as intermediate outcomes to model future behavioral change. Multiple predictors with empirical support are available from social-cognitive theories.

Furthermore, in health promotion adequate effectiveness data of innovative interventions are often lacking [6]. In case of many promising interventions the available data are inadequate for CEAs due to a variable follow-up length or a lack of validated behavioral endpoints. Yet, in many of these cases effects on cognitive variables, such as intention, are available. Modeling of cognitive parameters may provide a way to overcome variations between studies, by estimating the required behavioral endpoints for use in CEAs. For this method the focus is not on the health effects on the long term, but rather on reducing the risk factor (i.e. behavior) that might cause the disease. The presented method could therefore serve as an extension of several predictive simulation models for disease progression and death, such as for COPD [31,53,54]. Currently, these models use behavioral intermediate outcomes, such as smoking status, to predict future effects. However, in case these endpoints are missing or seem inadequate to describe full behavioral endpoints of an intervention due to delayed effects, they may be substituted or predicted by cognitive parameters. Ultimately, modeling future behavioral change can have important consequences for health policy development in general and the adoption of behavioral interventions in particular.

Aim of this thesis

In this dissertation the feasibility and validity of modeling cognitive parameters into CEAs of behavioral interventions were explored. The following goals were addressed in the present thesis:

1. To improve accuracy of current CEA methodology specifically for behavioral interventions;
2. To enable CEAs in behavioral interventions when objective physical behavioral data are lacking or insufficient;
3. To develop a feasible CEA modeling strategy that can be applied to interventions for different health behaviors;

And in order to facilitate the first three goals:

4. To validate assumptions of the predictive value of cognitive determinants by enabling a dynamic analysis of repeated measures of cognitive variables and behavioral outcome measures.

The research question that this dissertation aimed to address is:

Can cognitive parameters be included in CEAs of behavioral interventions to model future behavioral change, and is this a valid method to deal with issues like delayed behavioral change and insufficient effectiveness data for CEAs?

Outline of the thesis

The first study that is presented in this thesis gives an overview of the available scientific knowledge about the current role of cognitions in CEAs of behavioral intervention. In *chapter 2* a systematic review was performed [55]. In this review the goal was to identify which cognitive parameters of behavioral change can be distinguished in CEAs and to evaluate whether and how these parameters are incorporated in CEAs. *Chapter 3* presents the CEA of the SMOKE study [56,57]. This multicenter randomized controlled trial compared a high intensive smoking cessation intervention with a medium intensive smoking cessation intervention for COPD outpatients. In the next chapter, the same dataset was used to replicate this CEA with a predictive, model-based analysis. To explore the feasibility of incorporating partial behavioral change in CEA, the study in *chapter 4* was performed. The CEA of the comparison between the smoking cessation interventions for COPD outpatients presented in *chapter 3* was re-analyzed [58]. The aim was to incorporate partial behavioral change in the CEA, by means of modeling the stages-of-change construct of the TTM. The original time horizon of 12 months was extrapolated to a future 24 months of follow-up by modeling future effects. The TTM is a stage-oriented theory of behavior change. To explore inclusion of cognitive parameters in CEA derived from non-stage-based theories, more preliminary research on its predictability and fluctuations over time is needed. Therefore, in *chapter 5* time-varying cognitive parameters derived from the ASE Model [47] in the SMOKE study [56] were analyzed, additionally controlling for smoking status at time of assessment using Cox regression analyses. In *chapter 6* this same procedure was replicated to explore the time-varying association of cognitive parameters with smoking status in two separate, but similar datasets on smoking cessation intervention in cardiac patients [59,60]. Both studies provided a similar intervention (the C-MIS) to their intervention groups among cardiac in- and outpatients respectively. Consequently, results could be compared and validated between datasets. *Chapter 7* describes a study in which partial behavior change was incorporated in CEA by modeling cognitive parameters of behavior change derived from a non-stage-based theories of behavior change. The applied predictive model in this study was validated by comparing its outcomes with the true observed data. Data from the PAS study was used [61], which consists of a three-armed randomized controlled trial comparing two Internet-based smoking cessation interventions with usual care. Finally, in *chapter 8* the results of the presented studies are discussed as well as the implications, methods used and the value of the results for behavioral interventions and health policy in general.

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The role of cognition in cost-effectiveness analyses of behavioral interventions

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Abstract

Background. Behavioral interventions typically focus on objective behavioral endpoints like weight loss and smoking cessation. In reality, though, achieving full behavior change is a complex process in which several steps towards success are taken. Any progress in this process may also be considered as a beneficial outcome of the intervention, assuming that this increases the likelihood to achieve successful behavior change eventually. Until recently, there has been little consideration about whether partial behavior change at follow-up should be incorporated in cost-effectiveness analyses (CEAs). The aim of this explorative review is to identify CEAs of behavioral interventions in which cognitive outcome measures of behavior change are analyzed. *Methods*. Data sources were searched for publications before May 2011. *Results*. Twelve studies were found eligible for inclusion. Two different approaches were found: three studies calculated separate incremental cost-effectiveness ratios for cognitive outcome measures, and one study modeled partial behavior change into the final outcome. Both approaches rely on the assumption, be it implicitly or explicitly, that changes in cognitive outcome measures are predictive of future behavior change and may affect CEA outcomes. *Conclusion*. Potential value of cognitive states in CEA, as a way to account for partial behavior change, is to some extent recognized but not (yet) integrated in the field. In conclusion, CEAs should consider, and where appropriate incorporate, measures of partial behavior change when reporting effectiveness and hence cost-effectiveness.

Introduction

Resources in health care are generally limited. Consequently, funding priorities have to be set, preferably based on information that concerns the effectiveness and efficiency of available alternatives. In the health care systems in developed countries, cost-effectiveness analyses (CEAs) have become an accepted method to assess and improve the efficiency of pharmaceutical treatments [1,2] as in the field of health psychology and health promotion.

Performing a CEA on a health promotion intervention, however, has some implications for the CEA methodology compared to pharmaceutical interventions. Generally, health promotion interventions are designed to accomplish behavior change. CEAs of these interventions typically focus on objective behavioral data, i.e. physical endpoints like weight loss or biochemically validated smoking cessation [3,4]. In reality, though, behavior change is a complex process in which several steps towards success are taken, including changes in cognitive antecedents of behavior. Any progress in behavior change without accomplishing full behavior change may also be considered as a beneficial outcome of an intervention, assuming that this increases the likelihood to achieve successful behavior change eventually [5]. Adding partial effects can therefore improve the structure of CEA models in the field of health promotion. Butler et al. concluded from their study on smoking cessation that *'…focusing on quitting alone may understate efficiency on a wider range of related objectives such as reducing addiction or moving smokers towards the 'action' end of the stages of change continuum'* [6]. Similarly, Wagner & Goldstein argued that analysts who conduct a CEA of a behavioral intervention should not focus solely on people who successfully changed their behavior, but should also consider partial behavior change. Any progress in the process of behavior change caused by the intervention can then be included as a partial behavior change that may predict full behavior change in the future. Conversely, failing to include such partial effects in CEAs may bias the results [3].

Thus, in order to predict full behavior change after the study period ends, 'intermediate' outcomes of behavior change could be measured. Subsequently, modeling techniques like decision trees and Markov models are required to model these intermediate outcomes to final outcomes. Including intermediate outcomes in CEAs, though, has been subject of a large literature. The main counter argument is that a treatment can improve intermediate endpoints without (yet) improving the final health outcome [7]. Also, in these intermediate endpoints, important aspects of the intervention may not be caught. Thus, reliance on solely intermediate outcomes may over- or underestimate final outcomes [1]. Ultimately, the validity of intermediate outcomes in CEAs depends on the strength of the evidence that links the intermediate to the final health outcome of interest. The underlying assumption of intermediate or surrogate outcomes is that an intervention's effect on these endpoints predicts an effect on the outcome of interest. Although the terms 'surrogate' and 'intermediate' are sometimes used synonymously, there is a clear distinction. A surrogate outcome is not necessarily an intermediate step in a *causal* pathway, this in contrast to an intermediate outcome, and avoids any implication of causality [7]. Examples are prostate-specific antigen in prostate cancer as the indication of an advanced tumor stage [8] and morbidity as surrogate for mortality. In this case a causal relationship between intermediate, partial behavior change and full behavior change is a precondition to be able to predict future behavior. This precludes the use of surrogate outcomes within the scope of this paper.

Cognitive determinants of behavior can predict health behavior change and progression (or decline) in these determinants can also been seen as partial behavior change. These outcome measures are derived from theories, which are used to explain and predict behavior (change) and to guide the development and refinement of health promotion and education efforts [9]. Cognitive outcome measures are antecedents of behavior change, and can therefore be measured at some intermediate time point to predict health behavior in the future. Examples are psychological constructs such as attitudes, self-efficacy, risk perception, and social support. Previous research has demonstrated convincingly that several theories are successful in predicting a wide range of health behaviors [10,11].

The empirical basis for these constructs can be found in for example the Transtheoretical model of behavior change. This stage-oriented model describes the readiness to change [12]. It has been widely adopted for numerous health behaviors, but was originally designed to describe addictive behaviors and was based on research of self-initiated quit attempts by smokers [13]. A number of qualitatively different, discrete stages are key constructs of the Transtheoretical model. It provides an algorithm that distinguishes six stages, of which five are often used: 1) pre-contemplation (e.g. no intention to quit smoking within the next six months); 2) contemplation (e.g. intending to quit smoking within the next six months, but not within the next month); 3) preparation (e.g. intending to quit smoking within the next 30 days [13]); 4) action (e.g. being abstinent for less than six months); and 5) maintenance (e.g. being continuously abstinent from smoking for more than six months). The first three *pre-action* stages reflect stages of partial behavior change. Each pre-action stage provides probabilities for the *actual* transition to the fourth stage, the 'action stage' in which full behavioral change is achieved. The stage algorithm has been developed on the basis of empirical findings. Usually, attempts to modify (addictive) behavior are not immediately successful. With smoking, for example, successful quitters make an average of three to four attempts and go through a spiral pattern of several cycles before they reach long term abstinence. Relapse and recycling through the stages therefore occur quite frequently as individuals attempt to modify or cease addictive behaviors [13]. To classify participants according to their stage-of-change, questionnaires have been developed to assess readiness to change in individuals. Another example is the Theory of Planned Behavior [14], which is one of the most influential theories and has been used to predict many health behaviors successfully. It proposes that certain behavior can be predicted by a person's intention to perform that behavior. This behavioral intention in fact is closely related to the 'stages-of-change'-construct. According to the theory, the behavioral intention in turn is determined by a positive attitude towards smoking cessation, a high perceived behavioral control to refrain from smoking, and a high perceived social norm to stop smoking [15]. These psychological constructs are generally assessed with multiple-item questionnaires using Likert type scales. Self-reported scores of respondents are summated to a score on a unidimensional scale. An important distinction between stage theories such as the Transtheoretical model and social cognitive theories such as the Theory of Planned Behavior is that the former classifies subjects according to a discrete (dichotomous) stages-of-change algorithm, while the latter consists of dimensional variables that predict and explain behavior change.

Overall, the aforementioned social-cognitive determinants could be used as outcome measures reflecting partial behavior change which could be incorporated in CEAs - assuming adequate predictive value for the study of interest. This requires the combined expertise from the fields of health psychology and health economics. Although these disciplines share many goals (e.g., increasing healthy behaviors [16]), collaboration has been limited on this particular issue.

The aim of this explorative review is to identify CEAs of behavioral interventions in which cognitive outcome measures of behavior change are analyzed. The goals of the present review are: 1) to identify which cognitive outcome measures of behavior change can be distinguished in CEAs; and 2) to evaluate whether and how these outcomes are incorporated in CEAs.

Methods

All studies that conducted a cost-effectiveness (CEA), cost-utility (CUA) or cost-benefit analysis (CBA) and additionally included or reported cognitive outcome measures of behavior change were considered for inclusion in this review. Interventions to accomplish behavior change were compared to usual care or to an alternative intervention in these selected analyses.

Electronic databases (ScienceDirect, Scopus, Medline, Web of Science, HEED, EMBASE and PsycInfo) were searched for English or Dutch language publications that were published before May 2011 by standardized search strategies. The core search strategy used for this review was as follows: 1) ICER or cost-effectiveness or cost-utility or cost-benefit; 2) 1 and health; 3) 2 and behav*; 4) 3 and (model* or cogn*). Due to the exploratory character of this review, a broad search strategy was employed. Titles and abstracts of all citations generated from the search were assessed meeting inclusion and exclusion criteria to identify eligible publications. To identify additional publications, hand searches of reference lists were conducted. Studies that report costs and effects in a disaggregated way were excluded as this review aims to explore the methodology of applying cognitive outcome measures in CEA.

Data from eligible studies were entered into a matrix. Collected characteristics were the author(s) and year of publication, the study topic, a short description of the intervention, the effectiveness measure for CEA, the cognitive (intermediate) outcome measures of behavior change, the type of behavioral model used and a short description of the application of the cognitive outcome measure in the study (Table 1). The elements of the economic evaluations were not assessed in this review, as the focus was not on the actual final results of the analyses. Additionally, sufficient evidence for the validity of included cognitive intermediate outcomes of behavioral change needs to be available. Therefore, the validity was examined by considering the theoretical foundation of the reported cognitive outcome measures. If these are derived from empirically well-tested theories, a causal relation may be assumed. For this review, we consider this to be a prerequisite for a cognitive intermediate outcome to be valid.

Results

Of the 5,916 studies identified, 137 were qualified for the final selection. After the inclusion and exclusion criteria were applied by the reviewers, 12 CEAs and CUAs were identified that reported cognitive outcome measures of behavior change and therefore were eligible for review. Seventy eight studies were excluded for not reporting data on cognitive outcome measures of behavior change. Three studies were excluded as the function of the cognitive outcome measures was solely for design purposes of the intervention and not the CEA. In six studies the interventions were not aimed at behavioral change and in six other studies the authors had retrieved their results through meta-analyses. Furthermore, eight publications consisted of a study protocol or model development and in three studies there were no interventions described. Also, 21 studies were excluded for only reporting effects, and for reporting cost and effects separately.

In Table 1 details of the 12 included studies are shown. The included studies can be assigned to two categories describing the application of the cognitive outcome measures in these studies. The first category describes studies that integrated cognitive outcome measures in CEA. The second category contains studies that reported cognitive outcomes which were merely used as secondary outcomes of the intervention. In this last category of studies the cognitive outcome measures were not related to CEA.

Table 1. Characteristics of included studies

Authors	Topic	Intervention	Effectiveness measure	Cognitive outcome measures	Behavioral model used	Application of cognitive outcome measures
Butler 1999 [6]	Smoking cessation	Motivational consulting with brief advice	Smoking cessation, reduction in addiction and quit attempts	Stages-of-change	Transtheoretical model, self-efficacy theory	Effectiveness was calculated per stage-of-change at baseline and cognitive outcomes were used as secondary outcome measures
Crane 2000 [17]	Mammography screening	Multiple outcall approach	Mammography screening	Stages-of-change, attitude and knowledge	Transtheoretical model	Cognitive outcome measures were used to describe the theoretical foundations of the intervention and as secondary outcome measures
Emmons 2005 [18]	Smoking cessation	Peer counseling or self- help intervention	Smoking cessation	Stages-of- change, self-efficacy, perceived vulnerability, social support and knowledge	Transtheoretical model, social ecological model	Cognitive outcomes were used as secondary outcome measures
Kyle 2008 [19]	Sun protection	Sun protection education for young children	Nonfatal cases and premature mortalities averted and QALYs saved	Knowledge, attitude and intention	No theoretical foundation in model	Cognitive outcomes were used as secondary outcome measures

(continues)

Table 1. Characteristics of included studies **(continued)**

Authors	Topic	Intervention	Effectiveness measure	Cognitive outcome measures	Behavioral model used	Application of cognitive outcome measures
Lo 2009 [20]	Self-care behavior for stoma patients	Multimedia learning education program	Knowledge, attitude and behavior of self-care	Knowledge and attitude of self-care	No theoretical foundation in model	The effectiveness measure was a combined score of knowledge, attitudes and behavior of self-care
Oldenburg 1995 [21]	CVD risk reduction	CVD risk reduction programs	Unweighted CVD lifestyle risk scores	Stages-of-change	Transtheoretical model, social learning theory	Stages-of-change were used to appoint follow-up periods
Rasu 2010 [23]	Weight management	Internet-based weight management program	Change in body weight, a weight change of 5% or more, and waist circumference	Social pressure	No theoretical foundation in model	CE ratio was calculated for each additional point gain on Social Pressure subscale, indicating increased confidence in managing social pressures to eat
Pyne 2005 [22]	Patient receptivity to anti-depressants	Evidence-based primary-care depression intervention	QALYs	Attitude	No theoretical foundation in model	Two separate CE ratios were calculated for both negative and positive attitudes toward antidepressants
Saywell 1999 [24]	Compliance mammography Screening	Counseling strategies	Increase in mammography rate	Intention to screen	Health Belief Model	Cognitive outcome was used as secondary outcome measure

(continues)

Table 1. Characteristics of included studies **(continued)**

Authors	Topic	Intervention	Effectiveness measure	Cognitive outcome measures	Behavioral model used	Application of cognitive outcome measures
Sims 2004 [25]	Changing GP's behavior	Organized approach to exercise counseling	Amount of patients screened, activity, accruing health benefit, DALYs and premature deaths averted	Knowledge and attitude	No theoretical foundation in model	Cognitive outcomes were used as secondary outcome measures
Smith 2007 [26]	Smoking cessation	Multi component expert system intervention	Quit smoking	Stages-of-change	Transtheoretical model	An ICER was calculated that incorporated partial behavioral change as measured by the stages-of-change
Sood 2006 [27]	HIV/ AIDS prevention	Entertainment-education-based mass media campaign	Condom use frequency and changes in cognitive parameters of behavior change	Knowledge, gender attitude, and perceived risk	Multiple stage models of behavior change	Cost-effectiveness was calculated for condom use frequency and additionally for changes in the three cognitive outcome measures

Note. Year = year of publication, GP = general practitioner, CEA = cost-effectiveness analysis, CE ratio = cost-effectiveness ratio, ICER = incremental cost-effectiveness ratio, CVD = cardiovascular disease, QALY = quality adjusted life year, DALY = disability adjusted life year.

Incorporated in CEA

Four studies integrated cognitive outcome measures of behavior change in the CEA [22,23,26,27]. First, one study modeled partial behavior change measured by stages-of-change construct (Transtheoretical model) into the ICER. Smith et al. studied the incremental (cost-)effectiveness of a computerized smoking cessation intervention for primary care physicians. The mean ICER was $1,174 per LYS ($869 per QALY). However, the authors additionally considered the intervention impact on progression in stages-of-change. By advancing a smoker’s stage-of-change and adjusting for a 45% relapse rate, partial behavior change was incorporated in the ICER [17]. Consequently, this ratio declined 15% to $999 per LYS ($739 per QALY).

Second, three studies were found that calculated different ICERs for effects on cognitive outcome measures of behavior change. These papers applied a fundamentally different approach than Smith et al.: in these studies between-group differences in ICER outcomes were calculated by performing CEAs within subgroups [22] or separate ICERs were calculated for cognitive outcome measures in addition to the ICER for the behavioral outcome measure [23,27].

Pyne et al. studied the impact of patient treatment attitudes on the cost-effectiveness of healthcare interventions. The cognitive outcome measure attitude has been described as part of many social cognitive theories (e.g. Theory of Planned Behavior). The study estimated the impact of patient receptivity to antidepressant medication on the cost-effectiveness of an evidence-based primary-care depression intervention. Among patients receptive to antidepressants, the mean incremental cost-effectiveness ratio (ICER) was $5,864 per QALY, and was negative for patients non receptive to antidepressants [22]. Rasu et al. evaluated the cost-effectiveness of a behavioral Internet treatment program for weight management compared with usual care in a diverse sample of overweight adults in the United States Air Force. The ICERs for the primary outcomes indicated that the costs to lose one additional kilogram of weight, lose one additional centimeter of waist circumference, and make one additional 5% or more weight change were $25.92, $28.96 and $3.12 respectively. Additionally, an ICER was calculated for the cognitive outcome measure social pressure. For each additional point gain on the Social Pressure subscale (Weight Efficacy Lifestyle questionnaire), where increasing scores indicated increased confidence in managing social pressures to eat, the cost was $37.88 [23]. Sood & Nambiar examined the impact of exposure to entertainment-education-based mass media campaigns to prevent HIV. The cost-effectiveness was calculated for different components of the campaign for the behavioral outcome condom use. Additionally, cost-effectiveness was calculated for changes on measures of the cognitive outcome measures knowledge, gender attitudes and perceived risk [27].

In contrast to the other studies reported above [22,23,27], yet another approach is used to account for partial behavior change by Oldenburg et al. [21]. They focus on the difference between the two ‘action stages’, by comparing short-term behavior change (<six months) as outcome with long-term (>six months) behavior change. Thus, these authors did not predict future behavior change by modeling cognitive outcome measures like Smith et al., but they collected outcomes at six and 12 months for the interventions and calculate ICERs at both stages. In other words, they examined the economic aspects of the action and maintenance stage of lifestyle change to reduce cardiovascular disease. Instead of using the *patient's* stage-of-change as Smith et al. did in their study, they calculated different ICERs of a *program's* stage-of-change. Results showed that depending on the follow-up period, cost-effectiveness results varied. For the analysis of cardiovascular risk reduction during the ‘action phase’ (six months), the least expensive program, health risk assessment (HRA), was not effective in initiating change at all, and the most expensive program in the base assessment of costs, behavioral counseling plus incentives (BCI), was the least cost-effective. Behavioral counseling (BC) cost only marginally less than BCI, but proved to be almost twice as clinically effective and was considerably more cost-effective. Risk factor education (RFE) cost half that of BCI, yet was equally effective in terms of lifestyle change and was at a similar level of cost-effectiveness to BC. However, when the maintenance of the effects of the interventions was assessed 12 months after the start of the interventions (maintenance stage), the cost-effectiveness of the programs differed from the costs at six months follow-up. Only BC demonstrated significant risk reduction with little loss of cost-effectiveness from the earlier results. Both BCI and RFE were ineffective in sustaining change. For the BC intervention there was minimal relapse up to the 12 months follow-up and consequently emerged as the most cost-effectiveness intervention on the longer term. This study reveals that behavioral interventions may turn out to be more cost-effective when the probability of maintenance of behavior change is increased (or relapse to pre-action stages-of-change is prevented) [21].

Secondary outcome measures

In the second category cognitive outcome measures were reported as secondary outcomes of the intervention, without relating these outcome measures to the CEA. In seven studies the cognitive outcome measures of behavior change served as secondary outcome measures of the intervention [6,17–20,24,25]. The stages-of-change served as secondary outcomes in Butler et al. They assessed whether the effects of motivational consulting on smoking cessation were modified by subject's prior stage-of-change [6]. Also, in the study of Crane et al. the stages-of-change for mammographic screening served as a secondary outcome measure as well as for intervention design. In addition, knowledge, attitudes and perceived barriers toward mammographic screening were measured [17]. Emmons et al. report on the outcomes of a smoking cessation intervention for smokers in the 'Childhood Cancer Survivors Study'. Their interest was the extent to which several psychosocial factors were predictive of smoking cessation outcomes. Self-efficacy, stages-of-change, perceived vulnerability, social support and knowledge were also measured besides the quit rates for smoking [18]. Kyle et al. report the results of an economic analysis on a school-based sun safety education program. Secondary outcomes were knowledge, attitudes and intention towards sun protection behaviors [19]. Lo et al. compared the costs and effectiveness of enterostomal education using a multimedia learning education program and a conventional education service program. The effectiveness measure consisted of a combined score of knowledge of self-care, attitude of self-care and behavior of self-care. The cost measures for each patient were: health care costs, costs of the multimedia learning education program, and family costs [20]. Cost-effectiveness of five combinations of physician recommendation and telephone or in-person individualized counseling strategies for increasing compliance with mammographic screening was examined by Saywell et al. Besides an increase in mammography rate, the intention to screen was measured [24]. Sims et al. conducted a CEA on the 'Active Script Program' that aimed to increase the number of general practitioners who deliver appropriate, consistent, and effective advice on physical activity to patients. General practitioners' knowledge and attitude towards providing such advice were the cognitive parameters used as secondary outcome measures [25].

Cognitive parameters as theory-based intermediate outcomes

For all studies, the theoretical foundation of the cognitive outcome measures was judged, as reported in the selected articles. Five studies measured cognitive outcome measures of behavior change before and after the intervention, without explicitly describing a theoretical foundation of these outcome measures [19,20,22,23,25]. It is therefore not clear from these studies, whether the cognitive outcomes reflect true intermediate outcome measures. Kyle et al. measured knowledge, attitude and intention towards sun protection behavior among young children [19]. Lo et al. measured knowledge and attitudes of self-care behavior for stoma patients [20]. Pyne et al. reported attitude towards antidepressant medication as parameter of major depression [22]. Rasu et al.

measured social pressure in weight management which indicates the confidence in managing social pressures to eat [23]. Sims et al. measured knowledge and attitude of general practitioners regarding counseling patients on physical exercise [25].

Five studies reported different stages of the Transtheoretical model as parameters of behavior change [6,17,18,21,26]. These studies reported stages-of-change towards smoking cessation, except Crane et al., who reported stages-of-change towards participation in mammographic screening.

Two studies reported other theories of behavior change that provided cognitive outcome measures for their studies [24,27]. Saywell et al. conducted a study on mammographic screening and additionally measured the intention to screen, which was derived from the Health Belief Model [24]. Sood & Nambiar measured the parameters HIV knowledge, gender attitudes and perceived risk of HIV/AIDS, which were constructs of multiple stage models of behavior change, i.e. McGuire's hierarchy of effects, the stages-of-change model, steps to behavior change, Rogers's innovations decision model and Kincaid's ideation theory [27].

Discussion

Current CEA research of behavioral interventions predominantly relies on behavioral outcome measures. However, these do not take into account delayed behavior change that may occur after the follow-up period ends, and may consequently underestimate cost-effectiveness of psychological interventions. Furthermore, RCTs in the field of health promotion often are limited by a relatively short follow-up, increasing the likelihood of missing delayed effects. To remedy this, delayed intervention effects should somehow be incorporated in CEA. A number of empirically well-tested social-cognitive theories are available that enable prediction of future behavior change based on valid cognitive outcome measures, such as self-efficacy expectations [14,28-30]. Progression on these cognitive outcome measures can be seen as a beneficial outcome of an intervention, assuming that such a cognitive progression precedes behavior change. By broadly examining literature we explored whether there is potential for including cognitive outcomes in CEAs of health promotion, and what techniques are known to perform this. We found that the use of cognitive outcome measures in calculating ICERs is to some extent recognized, but is still in its infancy. The cognitive outcomes in the studies found served mainly as secondary outcome measures of the intervention and were not considered for CEA, except for four studies [22,23,26,27]. Two different frameworks for incorporating cognitive outcome measures preceding behavior change were distinguished from these results.

In the first framework the projected final outcomes are modeled based on cognitive outcome measures of behavior change. In the study of Smith et al. cognitive outcome measures were used to make a prediction of future behavioral change over time as a consequence of the intervention [26]. Besides modeling the stage-of-change, Smith et al. also adjusted for future relapse of quitters to smoking in the CE ratio. In spite of this conservative approach, results showed a 15% decline of the CE ratio compared to the ratio that included only observed quitters at the end of the study period.

In the second framework cognitive outcome measures of behavior change are simply applied as alternative or secondary intervention outcomes in a CEA. Three studies qualified for this category [22,23,27]. These did not include partial behavior change by predicting future behavior change in the CEA as shown by Smith et al., but calculated ICERs for cognitive parameters as outcome measure of the intervention. Thus, these studies calculated different ICERs for different cognitive states. Importantly, both frameworks assume that improvements in cognitions eventually result in behavioral change. When an intervention results in significant changes in valid cognitive intermediate outcomes, it is assumed to be more likely that behavior change will occur later on as a result of this cognitive change. However, in contrast to the first framework, this assumption remains more implicit in this second framework. It would be informative to include separate ICERs for significant cognitive outcome measures in addition to or even as a substitute for the original ICER. Moreover, as the study by Smith et al. showed, incorporating cognitive outcome measures in CEA may produce results deviating from standard CEA methods that do not directly recognize the effect of behavioral change. This emphasizes the need to further explore the role of cognitive outcome measures in CEA. Also, it is unclear which framework (modeling future behavior change or calculating ICERs for cognitive outcomes) is preferred under which conditions. The approach of Smith et al. seems potentially more promising as it is a more sophisticated method to incorporate partial behavioral change. It also seems a more transparent approach as it makes the assumption that changes in cognitions eventually result in behavioral change more explicit, and enables sensitivity analyses of the parameters in the model. Moreover, this approach takes one step further: in this case cognitive outcome measures are used to estimate future behavior change in a prognostic model. This makes it also more demanding and complex, as the predictive value of the cognitive outcome measures is crucial for the validity of the results. A strong theoretical model can help to justify the choice for cognitive outcome measures as intermediate outcomes. Concerning the psychological theories described in this review, there has been some discussion in literature about the predictive validity of the Transtheoretical model. However, this discussion mainly concerns its supposed usefulness for designing stage-based, tailored interventions with superior effectiveness [31-33]. It has been the predictive validity of the stages-of-change construct itself that has received high empirical support [34,35]. Also, literature on, for example, the Theory of Planned Behavior provides ample evidence supporting the use of this theory for predicting behavior [10]. Other empirically well-supported health behavior theories are the Health Belief Model [28], the Theory of Reasoned Action [29], and Social Cognitive Theory [30]. There are models specific to behavioral areas such as safer sex [36] and alcohol use [37], as are integrated theories combining constructs from multiple theories [38,39]. Overall, many theories are available in literature that describe and predict health behavior change [40]. However, as the predictive value of cognitive constructs from these models will not be perfect, like most prediction models in CEA literature, sensitivity analyses remain essential in such economic evaluations in order to assess reliability of CEAs.

There are also some methodological issues that need to be considered. Firstly, the Transtheoretical model [13] distinguishes different stages of behavioral change and empirical data provide transition probabilities to predict movement through these stages. By means of Markov modeling, transition probabilities of moving to and from the 'action' or 'maintenance' stage, can predict the percentage of additional quitters and additional relapsers on the long term. For incorporating partial behavior change like Smith et al. [26], these additional quitters and relapsers can be added to or subtracted from those who already have accomplished full behavioral change at follow-up. For smoking cessation, the effects of the intervention will probably increase (as long as the rate of future quitters exceeds the rate of future relapsers), while the costs of the intervention remain constant. Consequently, the CE ratio decreases. However, for other behaviors than smoking, the empirical support for transition rates may not be equally robust. Furthermore, the transition probabilities may depend on several context variables, such as the population, the comparative intervention and the exact point in time at which behavioral change (or relapse) may occur. Lastly, the stage-oriented Transtheoretical model classifies individuals into discrete states. This enables the use of a Markov model, as this technique is based on multiple health states [41]. Many research is available describing the transition probabilities for the stages of change of the Transtheoretical model. The Theory of Planned Behavior does not distinguish qualitatively different states, but provides a multidimensional change continuum. In Markov modeling, this would require an almost indefinite number of health states. Probably, other decision analytic techniques like discrete event simulation may be needed to model continuous cognitive outcome measures to future behavioral change [42].

This raises another methodological issue. Scales used for cognitive outcome measures are usually based on 5-point Likert scales, which are in principle considered to produce ordinal data. However, there appears to be consensus in methodological literature that analyses based on 5-point scales in general result in findings similar to data obtained with interval scales, and may therefore be accepted in such analytical techniques [43-45].

Accounting for cognitive outcome measures of behavior may be advisable for several reasons. Firstly, as already outlined in the introduction, it is likely that delayed effects of behavioral interventions may occur due to relatively short follow-up periods. Ignoring delayed effects, may negatively bias CEA outcomes and, as a result, cost-effectiveness of behavioral interventions could be underestimated with current methodology. Oldenburg et al. already showed that cost-effectiveness results shift when exploring different follow-up periods, due to delayed effects and relapse [21]. Also, a review of Richardson et al. on cost-effectiveness of interventions to support self-care concluded that drawing general, reliable conclusions about the cost-effectiveness is problematic due to short follow-up periods [46]. Secondly, effectiveness data from existing trials that were not originally developed with the aim of a CEA are often unsuitable for CEAs due to a lack of adequate behavioral endpoints. However, if cognitive outcomes can serve as intermediate outcomes of behavioral change, these may be used in addition to or even as a substitute for current effectiveness outcomes. Obviously, which specific cognitive parameters are valid intermediate outcomes, depends on the behavior of interest and should be explored before consideration in CEA. Potentially, including cognitive outcome measures can make many more health promotion programs available for health economists to evaluate cost-effectiveness.

Considering limitations, some are of note. Firstly, the focus of this review is restricted to health promotion interventions aimed at behavior change. Search results covered a broad area of behaviors, ranging from smoking cessation to mammographic screening behavior and HIV/AIDS prevention. Multiple other areas could have been addressed, as cognitions are also known to precede, for instance, mental health states like depression. Including these studies would open a whole new area in which another range of cognitive outcome measures precede the final outcome (in this case mental health). However, due to its explorative character the scope of our review was limited to health promotion interventions aimed at behavior change, as delayed behavior change and studies on cognitive outcome measures are common and well known in this area. Second, studies reporting cost and effects separately in a disaggregated way were excluded from this review as such studies did not report an economic evaluation. However, such studies may provide additional information on the availability of studies with data that are, in principle, suitable for the proposed frameworks in this review.

Conclusions

From CEA literature in the field of health promotion two different frameworks were obtained that attempt to account for the complex process of behavior change in CEAs of behavioral interventions. Both frameworks assume that changes in cognitions, as antecedents of behavior, are predictive of future behavioral change. In the first approach, cognitive outcome measures were modeled to predict future behavior change and included in the ICER. In the second approach cognitive outcome measures were presented as effectiveness measures in CEAs. Importantly, CEAs that do consider cognitive outcome measures in their methods show that CEA may not capture the full impact of interventions if partial behavior change is not considered. This can be based on the different ICERs found in analyses that included cognitive outcome measures, when compared to standard CEA methods that do not directly recognize the effect of behavioral change.

The present review shows that the potential value of cognitive states in CEA, as a way to account for partial behavior change, is to some extent recognized, but not (yet) integrated in the field. In conclusion, CEAs should consider, and where appropriate incorporate measures of partial behavioral change when reporting effectiveness and hence cost-effectiveness.

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3

Cost-effectiveness of an intensive smoking cessation intervention for COPD outpatients

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Abstract

Background. To determine the cost-effectiveness of a high-intensity smoking cessation program (SmokeStopTherapy; SST) versus a medium-intensity treatment (Minimal Intervention Strategy for Lung patients; LMIS) for COPD outpatients. *Methods*. The cost-effectiveness analysis was based on a randomized controlled trial investigating the effectiveness of the SST compared to the LMIS with 12 months follow-up. The primary outcome measure was the cotinine-validated continuous abstinence rate based on intention-to-treat. A health-care perspective was adopted, with outcomes assessed in terms of (incremental) additional quitters gained, exacerbations prevented and hospital days prevented. Health care resource use, associated with smoking cessation, was collected at baseline and 12 months after the start of the interventions. Monte Carlo simulations were performed to evaluate the robustness of the results. *Results*. The average patient receiving SST generated €581 in health care costs, including the costs of the smoking cessation program, versus €595 in the LMIS. The SST is also associated with a lower average number of exacerbations (.38 versus .60) and hospital days (.39 versus 1) per patient, and a higher number of quitters (20 versus 9) at lower total costs. This leads to a dominance of the SST compared to the LMIS. *Conclusion*. The high intensive SST is more cost-effective than the medium intensive LMIS after one year. This is associated with cost-savings per additional quitter, prevented exacerbations and hospital days at lower or equal costs.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality worldwide and is causally related to smoking. Typically, the disease does not present itself before the age of 40. The social and economic burden of COPD is considerable; both in terms of direct medical costs as well as indirect costs (e.g. lost productivity). Due to the substantial increase in tobacco use since World War II and the changing age structure, this global burden of COPD is likely to increase. However, economic evaluations concerning COPD are scarce [1]. Investments in the treatment of COPD seem to be the key activity to mitigate the present and future burden of COPD.

Smoking cessation is the only evidence based treatment to improve the COPD prognosis [2,3]. It does not reverse respiratory function loss, but decreases the annual decline in lung function, reduces symptoms of cough and sputum, improves health status and reduces exacerbations of COPD [4-6]. COPD patients have a long smoking history and most have experienced numerous unsuccessful previous quit attempts [7,8]. This makes smoking cessation even more difficult for this group. An effective smoking cessation program should therefore be targeted to these high-risk smokers. Several smoking cessation programs have been tested in COPD patients, with varying components and combinations of components, such as simple advice to quit, pharmacological therapies (nicotine replacement therapy (NRT), antidepressants, and varenicline), face-to-face counseling (brief or more intensive), and proactive telephone counseling. Depending on the strategy used, different smoking cessation rates can be found in literature, ranging from 8.8% for low intensity smoking cessation counseling to 34.5% for the combination of psychosocial and pharmacotherapy [9]. A combination of pharmacological and behavioral strategies is recommended for COPD smokers [9-11].

The SMOKE study is a randomized controlled multi-center trial with 12 months follow-up to evaluate the relative (cost-)effectiveness of a new intensive multi-component smoking cessation intervention for COPD outpatients, the SmokeStopTherapy (SST), compared to the Minimal Intervention Strategy for Lung patients (LMIS) [12]. The LMIS is adapted from the Minimal Intervention Strategy (MIS) developed for smoking cessation in general practice [13,14] and can be considered as the recommended practice in outpatient pulmonary medicine in the Netherlands; a treatment of medium intensity. Both programs consist of evidence-based elements which are also internationally well-known [15]. The LMIS consists of three individual counseling sessions (60 minutes the first meeting and 45 minutes each consecutive meeting) and three telephone contacts (10 minutes each). Pharmacological aids are allowed and at the patients' own expense. Within the LMIS group, 10% of the participants used NRT, 32% used bupropion, and 8% used both

NRT and bupropion. The SST contains four individual counseling sessions (60 minutes the first meeting and 45 minutes each successive meeting), four telephone contacts (10 minutes each), four small-group counseling sessions (90 minutes each), and pharmacological support is strongly advised (bupropion is provided free of charge and was mandatory for patients in the SST group). All counseling sessions were provided by pulmonary nurses. Next to bupropion, nicotine replacement therapy (NRT) was used by 14% in the SST group, and at the patients' own expense. Additionally, patients can 'recycle' (restart the individual sessions) in case of a lapse within three months. The intervention period of both LMIS and SST is three months. Within the SST, the intervention period may be extended up to six months when a patient 'recycles'. This occurred in 19% (22/114) of the SST participants. However, none of them reached abstinence from smoking at twelve months after the start of the intervention. After one year the continuous abstinence rate (salivary cotinine validated abstinence at six and 12 months) was 19% (20/105) in the SST and 9% (9/105) in the LMIS (RR=2.22; *95% CI:* 1.06-4.65; p=.03).

The current study tests whether introducing the more effective high-intensity program (SST) outweighs the additional costs compared to the currently preferred medium-intensity smoking cessation program (LMIS). Based on recommendations from previous research to intensify the LMIS in order to increase the success rates [16], the SST was expected to be more effective than the LMIS. As smoking cessation results in a decline in exacerbations among COPD patients and consequently in hospitalizations following these exacerbations, these results are hypothesized to be also cost-effective. Probabilistic decision analyses were performed to compare the cost-effectiveness of these interventions, when looking at costs per additional quitter and the costs per exacerbation and hospital days prevented over the 12-month time frame.

Methods

The SMOKE study is a randomized controlled multi-center trial with one year follow-up which evaluated the effectiveness of the SmokeStopTherapy (SST) compared with the Minimal Intervention Strategy for Lung patients (LMIS). A total of 234 patients motivated to quit smoking, (checked by their own chest physician), aged between 40-75 years at the start of the study, having no contra-indications regarding the use of bupropion, and clinically diagnosed moderate COPD (percentage predicted FEV1=50-69) to severe COPD (percentage predicted FEV1=<50) as defined by the American Thoracic Society (ATS) criteria [17], were included in the study and randomly assigned: 117 received the LMIS and 117 patients received the SST. The chest physician advised each smoking COPD patient to quit smoking and, after informed consent was received, referred to the SMOKE study. A total of nine patients dropped out after giving informed consent: six from the LMIS and three from the SST. At baseline, another 15 patients dropped out: six from the LMIS and nine from the SST. They were excluded from all analyses. In both conditions 105 patients remained for analyses. All missing patients at 12 months follow-up were assumed to be smokers. All remaining patients adhered to the counseling sessions.

Baseline characteristics are presented in Table 1. Three baseline differences were found between groups. Patients receiving medium-intensity treatment were older than those receiving the high-intensity treatment ($p<.05$). Nicotine dependence, as measured by the Fagerström questionnaire, was significantly stronger in the participants allocated to the high-intensity treatment compared to medium-intensity treatment ($p<.05$). In relation with this finding, the nicotine addiction, as indicated by the categorical outcome of the Fagerström questionnaire, was also stronger in the high-intensity treatment compared to the medium-intensity treatment ($p<.01$). In a previously published prospective analysis of predictors of quitting in this sample [18], these three baseline characteristics appeared not to be predictive of validated abstinence at 12 months follow-up. A bias due to these baseline differences is therefore unlikely.

The study was approved by the Medical Ethical Committees of all three hospitals (Medisch Spectrum Twente, Enschede, The Netherlands; Slotervaart hospital, Amsterdam, The Netherlands; Catharina hospital, Eindhoven, The Netherlands) and all patients gave informed consent.

Table 1. Baseline characteristics of 225 outpatients with COPD

Variables	Minimal Intervention Strategy for Lung patients (n=111)	SmokeStopTherapy (n=114)
Gender, Male / Female	63 (57%) / 48 (43%)	55 (48%) / 59 (52%)
Age, yr*	59.6 (8.51)	57.0 (8.41)
FEV_1, L	1.86 (.85)	1.93 (.91)
FEV_1 % predicted of normal	62.8 (25.7)	65.6 (27.4)
IVC, L	4.78 (8.45)	4.71 (7.88)
Cotinine value, ng/ml	292 (144)	324 (145)
Cigarettes daily	20.5 (13.5)	24.1 (13.8)
Pack-years	41.7 (23.9)	46.4 (25.4)
Previous quit attempts (>24hr)	2.89 (5.95)	2.47 (3.38)
Smoking environment, range 0-4	.97 (0.85)	.96 (.84)
Self-efficacy, range -2-2	.09 (.84)	.12 (.90)
Outcome expectancies, range -1.5-1.5	.61 (.54)	.52 (.48)
Social Influence, range 0-3	1.31 (.87)	1.49 (.90)
Quality of life (SGRQ) three domains, range 0-100		
Symptoms	52.2 (22.4)	51.4 (22.9)
Activity	55.6 (22.5)	54.6 (23.4)
Impacts	28.6 (16.8)	32.7 (19.8)
Total	40.7 (16.7)	42.5 (19.1)
Depression (BDI), range 0-63	12.1 (8.45)	9.84 (8.37)
Nicotine dependence (Fagerström), range 0-10**	4.98 (2.05)	5.84 (2.14)
Nicotine addiction (Fagerström score ≥6), Yes / No*	39 (42%) / 54 (58%)	58 (59%) / 40 (41%)
Education level		
High	20 (19%)	13 (13%)
Middle	32 (30%)	30 (31%)
Low	54 (51%)	54 (56%)

Note. *p<.05 **p<.01. Characteristics are presented as means (standard deviation) or numbers (%).

Economic evaluation

A decision analytic model with a time perspective of 12 months was developed to evaluate the cost-effectiveness of the SST versus the LMIS (Figures 1 and 2). The percentages are derived from the SMOKE study for each (upper) arm in the decision analytic model. For example, the percentage of the patients in the SST group having quit smoking (18.7%), using NRT (14.9%), experiencing an exacerbation (95.4%) and not having been admitted to the hospital (99.8%), was 2.7% (18.7% * 14.9% * 95.4% * 99.8%). The costs for this arm were €654, consisting of costs regarding the intervention, the NRT use, and the exacerbation.

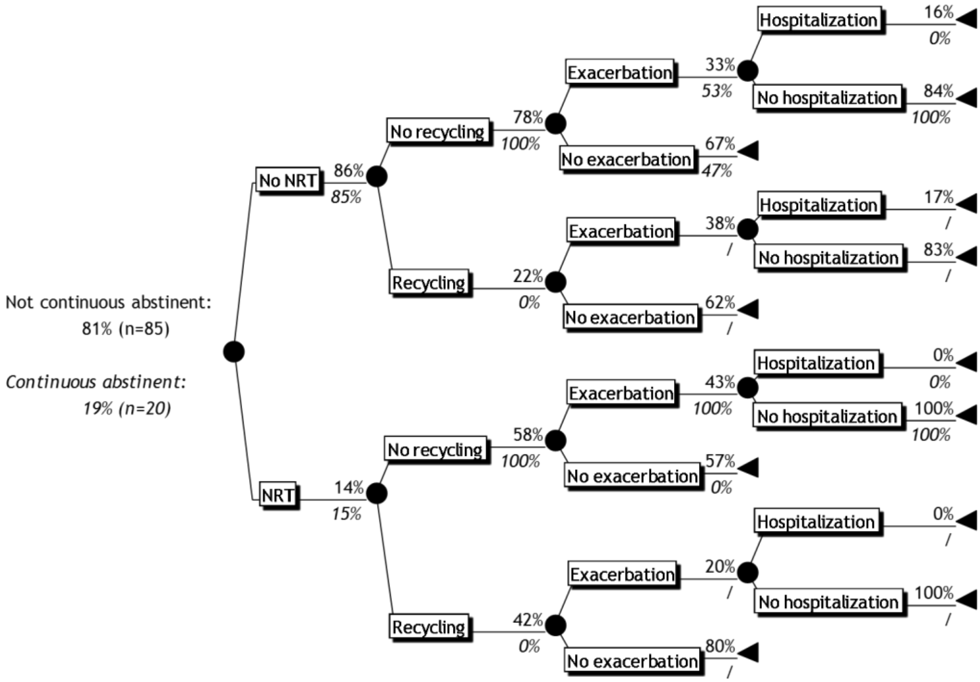

Figure 1. Decision analytic model; SmokeStopTherapy (SST) arm with distribution for both no continuous abstinence and continuous abstinence

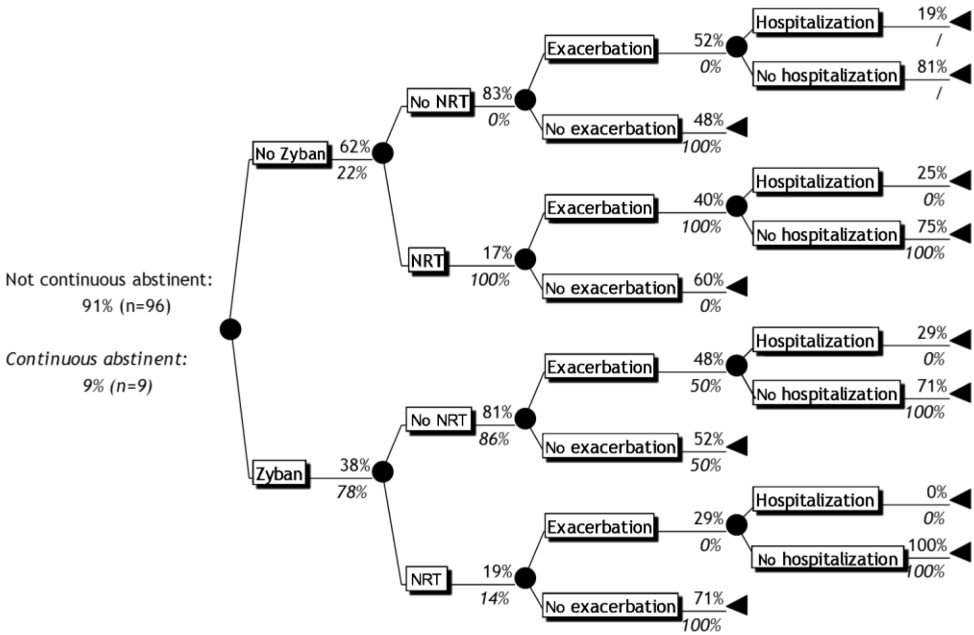

Figure 2. Decision analytic model; Minimal Intervention Strategy for Lung patients (LMIS) arm with distribution for both no continuous abstinence and continuous abstinence

All base case values of the probabilities with their 95% confidence intervals are presented in Table 2. We took the perspective of the health care payer, which mainly includes costs regarding the intervention components and medical expenses. Cost-effectiveness ratios were calculated for costs per exacerbation day prevented, costs per hospital days prevented, and costs per additional quitter.

Table 2. Base case values of the probabilities of each possible step in the decision tree

	Base case values of the SST (*95% CI*)
No CA	.81 (.73-.90)
No CA + No NRT + No R + Exa	.33 (.12-.55)
No CA + No NRT + No R + Exa + Hosp	.16 (.18-.58)
No CA + No NRT + R	.22 (.18-.43)
No CA + No NRT + R + Exa	.38 (.18-.77)
No CA + No NRT + R + Exa + Hosp	.17 (.08-.91)
No CA + NRT	.14 (.16-.79)
No CA + NRT + No R + Exa	.43 (.17-1.00)
No CA + NRT + No R + Exa + Hosp	.00*
No CA + NRT + R	.42 (.21-.86)
No CA + NRT + R + Exa	.20 (.34-1.00)
No CA + NRT + R + Exa + Hosp	.00*
CA + No NRT + Exa	.53 (.13-.86)
CA + No NRT + Exa + Hosp	.00*
CA + NRT	.15 (.18-.56)
CA + NRT + Exa	1.00**
CA + NRT + Exa + Hosp	.00*

(continues)

Table 2. Base case values of the probabilities of each possible step in the decision tree **(continued)**

	Base case values of the LMIS (*95% CI*)
No CA	.91 (.85-.97)
No CA + No Zyban + No NRT + Exa	.52 (.32-.72)
No CA + No Zyban + No NRT + Exa + Hosp	.19 (.19-.54)
No CA + No Zyban + NRT	.17 (.19-.40)
No CA + No Zyban + NRT + Exa	.40 (.39-.89)
No CA + No Zyban + NRT + Exa + Hosp	.25 (.22-1.00)
No CA + Zyban	.38 (.21-.54)
No CA + Zyban + No NRT + Exa	.48 (.42-.55)
No CA + Zyban + No NRT + Exa + Hosp	.29 (.18-.74)
No CA + Zyban + NRT	.19 (.17-.49)
No CA + Zyban + NRT + Exa	.29 (.24-.93)
No CA + Zyban + NRT + Exa + Hosp	.00*
CA + No Zyban + No NRT + Exa	.00*
CA + No Zyban + No NRT + Exa + Hosp	.00*
CA + No Zyban + NRT	1.00**
CA + No Zyban + NRT + Exa	1.00**
CA + No Zyban + NRT + Exa + Hosp	.00*
CA + Zyban	.78 (.46-1.00)
CA + Zyban + No NRT + Exa	.50 (.18-1.00)
CA + Zyban + No NRT + Exa + Hosp	.00*
CA + Zyban + NRT	.14 (.56-.29)
CA + Zyban + NRT + Exa	.00*
CA + Zyban + NRT + Exa + Hosp	.00*

Note. SST = SmokeStopTherapy; LMIS = Minimal Intervention Strategy for Lung patients; CA = Continuous Abstinence/ quitters, no CA = no Continuous Abstinence/ smokers; NRT= Nicotine Replacement Therapy; R= 'Recycling'; *95% CI* = 95% Confidence Interval; Exa = Exacerbation; Hosp = Hospital admissions; Zyban = Use of bupropion (Zyban®); *The assumption was made that the point value was .0025 for actual point values of 0; ** The assumption was made that the point value was .95 for actual point values of 1.

The primary outcome of the decision tree is the expected (incremental) costs of SST and LMIS per additional quitter. Secondary outcomes were prevented exacerbations and hospital days. An exacerbation was defined as recently having experienced one of the following: (a) a short course of prednisolone or antibiotics following deterioration of COPD, (b) a visit to the chest clinic or emergency room following deterioration of COPD or (c) a visit to the general practitioner following deterioration of COPD. Hospital days were defined as the mean number of days having been admitted to the hospital following deterioration of COPD. Both hospital days and exacerbations were measured during the lung function visits at baseline and at 12 months follow-up. Patients were questioned by a pulmonary nurse about the exacerbation treatment (e.g. hospitalization days and medication treatment).

Because our data originated from trial data, uncertainty relating to observed data inputs existed. For sensitivity analyses, Monte Carlo simulations with 1,000 iterations were performed to evaluate the relative impact of likely variations in the parameters of the decision analytic model. Therefore, cost probabilities and parameters were varied simultaneously over their ranges and the associated 95% confidence intervals. For the cost parameters a gamma distribution was used and logistic normal distributions were used for all probabilities.

Health care resource use and costs

The health care resource use was monitored during the 12 month follow-up period in which patients were questioned with regard to hospital admissions, experienced exacerbations, and the use of medication related to their quitting attempt (bupropion, NRT) (Table 3). Measurements regarding costs (medication use, hospital days, emergency room visits) were done at baseline (prior to the intervention) and at 12 months follow-up.

Table 3. Mean costs (€) per patient per event using 2002 cost price

Costs of hospitalization[a]	3,140
Costs per exacerbation consisting of:	101.25[b]
Pulmonary physician for 10 minutes	21.67
Lung function assistant for 20 minutes	8.39
Prednisole	11.70[c]
Other antibiotics[d]	10.37[c]
Lung function spirometry	29.90
Thorax X-ray picture	38.35
NRT use[e]	223.75
Recycling (SmokeStopTherapy) – four individual sessions	75.50

Note. [a]Cost per hospitalization day: €286 for normal care day and €1,243 of intensive care day; mean of 10.39 and .13 respectively. [b]Mean of minimal exacerbation costs excluding thorax X-ray picture €82.03 and maximal exacerbation costs including thorax X-ray picture €120.38. [c]Including €3 dispensing fee. [d]Usage for the trial's participants: 2% augmentin, 43% doxycycline, 44% amoxicillin, 11% clarithromycin. [d]Assumption based on: 50% patch (mean €190.50), 33.3% gum (costs €252.50), 16.7% patch (mean €266.50) for this patient group.

Use of medication related to an experienced exacerbation (prednisolone and antibiotics) was assessed from pharmacy records, containing all drugs used in the study period. The costs associated with the drugs were calculated using standards such as the Dutch Pharmacotherapeutical Compass [19]. Medication costs were based on market prices and included a €3 dispensing fee. Furthermore, the controllers of the hospitals were consulted regarding the prices for medical treatment and resource use, including the salaries of respiratory nurses, lung function assistants, and chest physicians at the time the treatment took place (2002). The costs associated with the use of bupropion are included in the intervention costs of the SST, but are counted separately within the LMIS group. In SST bupropion was prescribed to and used by all participants. In the LMIS group 30% of patients used bupropion. The total intervention costs are calculated at €379 for the SST and €97 for the LMIS, including salary costs of a respiratory nurse who executed the intervention and a referring chest physician (Table 4). Finally, the costs and effects were not discounted for time preference due to the short time frame of 12 months.

Table 4. Mean costs (€) intervention components per patient for SST and LMIS using 2002 cost prices

	SST			LMIS		
Intervention components	Mean volume	Unit costs	Mean costs	Mean volume	Unit costs	Mean costs
Telephone contacts[a]	.67 hr	25.18	16.79	.5 hr	25.18	12.59
Individual sessions[a]	3.25 hr	25.18	81.84	2.5 hr	25.18	62.95
Group sessions[ab]	6 hr	25.18	18.89	-		-
Referral and advice pulmonary physician	.17 hr	130	21.67	.17 hr	21.67	21.67
Zyban® course	180 pills	1.33[c]	240.17	-		-
Total costs			379.36			97.21

Note. [a]Consists of costs pulmonary nurse; [b]Groups consist of 8 patients; [c] €43.25 for 30 pills, €193.92 for 150 pills, €3 dispensing fee; hr = hours.

Results

Trial based cost-effectiveness analysis

The total annual costs of an average COPD patient within this trial following the SST was €581 compared with €595 in the LMIS. The costs of the SST were slightly lower and the SST achieved a larger number of quitters compared to the LMIS, implying cost-savings per additional quitter gained. The same was true for costs per additional exacerbation or hospital days. The average number of exacerbations was .38 within the SST group and .60

within the LMIS. The number of hospital days was .39 for patients receiving the SST compared to 1.0 for patients receiving the LMIS. The number of quitters is 20 (19%) in the high intensive SST versus 9 (9%) in the medium intensive LMIS and the associated costs are €3,101 per quitter in the SST and €6,832 per quitter in the LMIS. As the SST has dominancy over the LMIS on each outcome parameter, no incremental cost-effectiveness ratios were calculated (Table 5).

Table 5. Costs (€) and effects 12 months after the start of the SST and LMIS

	SST	LMIS
Costs		
Costs per quitter	3101	6832
Costs (per patient)		
Total costs	581	595
Costs of an exacerbation[a]	3.27	8.23
Costs of a hospital day[b]	27.93	124
Effects		
Number of quitters	20	9
Effects (per patient)		
Mean number exacerbations	.38	.60
Mean number hospital days	.39	1.00

Note. [a]Includes salary costs of a chest physician and lung function assistant, oral steroids and antibiotics including €3 prescription costs, spirometry costs and costs of a thorax X-ray in 50% of the cases. [b]Mean number of hospital days per hospital admission is assumed 10.5.

Sensitivity analyses of the decision analytic model

Probabilistic sensitivity analyses using Monte Carlo simulations were employed to analyze the robustness of the above mentioned findings for the time period of 12 months. To obtain a representative range of costs and effects, 1,000 iterations were used. The mean difference in total costs between both interventions after simulation is €12 (*95% CI*: €122-€104) in favor of the SST. The estimates of the costs and effects are presented graphically in Figure 3.

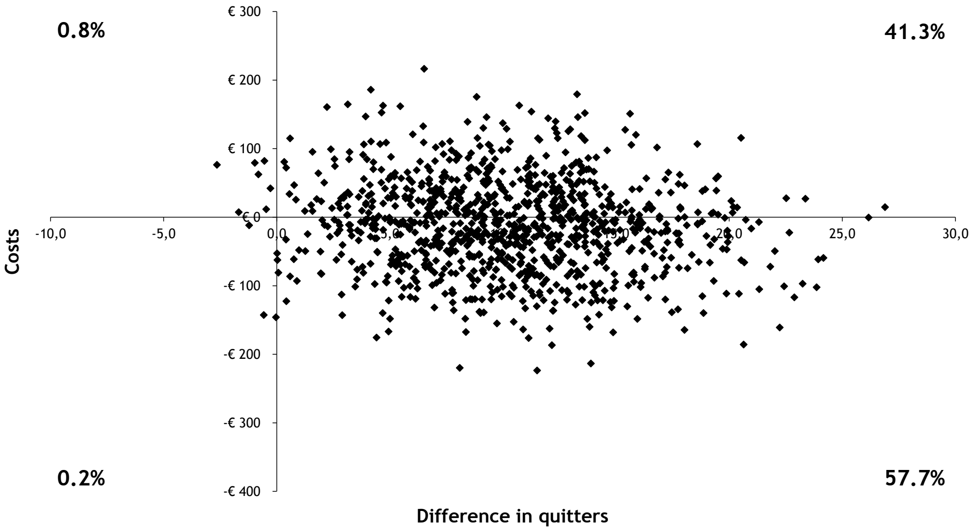

Figure 3. Monte Carlo simulation results for costs per additional quitter. A negative € amount and a positive difference in number of quitters favor the SST

The dominant outcome of the SST, meaning a positive treatment effect in combination with saving costs, was observed in the majority of the outcomes (additional quitters 57.7%, exacerbations prevented 57.7% and hospital days prevented 57.9%). Positive effects, independent of the costs, were seen in 90%, 97.2% and 99.9% of the iterations for the additional quitters, exacerbations and hospitalizations, respectively. The mean difference in the number of exacerbations per patient is -.23 (*95% CI*: -.46-.02). In 39.5% of the simulations, the SST prevents more exacerbations, but at higher cost (Figure 4). The mean difference in hospital days is -.60 (*95% CI:* -.91- -.27). In 42% of the simulations, the SST results in more prevented hospital days but also at higher cost (Figure 5).

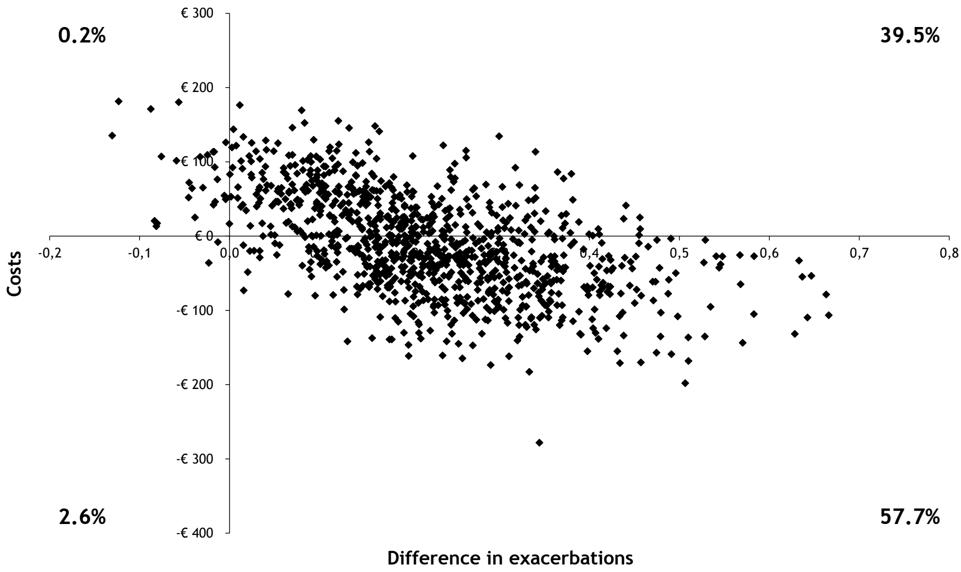

Figure 4. Monte Carlo simulation results for costs per exacerbation prevented. A negative € amount and a positive difference in exacerbations prevented favor the SST

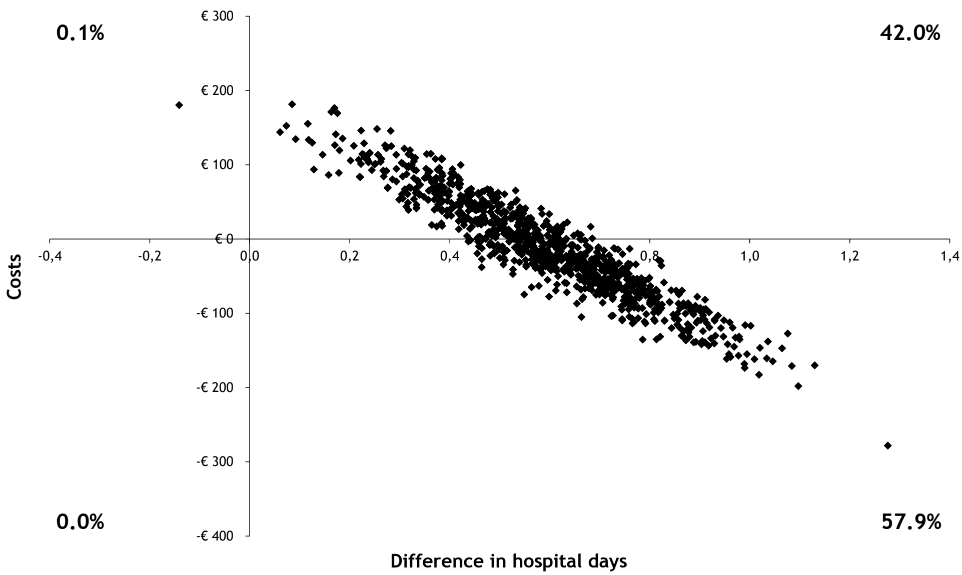

Figure 5. Monte Carlo simulation results for costs per hospital day prevented. A negative € amount and a positive difference in hospital days prevented favor the SST

The cost-effectiveness plane shown in Figure 3 represents the difference in costs associated with the difference in the number of quitters. In almost all simulations a higher number of quitters is associated with the SST. The mean difference in the number of quitters is 10.24 (*95% CI*: 2.68-18.66) and the mean difference in costs per quitter is €3.79 (*95% CI:* -€17.30-€13), both in favor of the SST. The percentages of outcomes in every quadrant are given.

Discussion

This study shows that a high-intensity smoking cessation intervention (SST) is cost-effective compared to a medium-intensive intervention (LMIS). The SST not only proves to be more effective, but in approximately 58% of all simulations even less costly and more effective and therefore dominates the LMIS over a one year follow-up. There are no additional costs but actually savings associated with additional quitters, prevented exacerbations and prevented hospital days. The data of this study were generated from a multi-center trial in three large general hospitals. This enhances the generalizability of the costs and the benefits found in the three hospitals. Based on this cost-effectiveness analysis, the SST is the preferred treatment compared to the LMIS and therefore attractive for decision makers in the health care context. Obviously, patients' preferences for treatment remain crucial for a successful implementation in health care.

This outcome deviates from previous reviews to a certain extent. Stead et al. [20] concluded in an updated Cochrane review that more intensive physician counseling is only slightly more effective than brief counseling. In the Surgeon General report a meta-analysis on counseling intensity concluded that intensity does have a dose-response effect on cessation up to 90 minutes contact time, but there appears to be no evidence that more than 90 minutes of contact time further increases quitting rates [21]. As both interventions in the current trial (LMIS = 180 minutes; SST = 595 minutes) exceeded this level of intensity considerably, our study may contribute to the scarce evidence on this point. Our results suggest that the dose-response effect does occur at levels of counseling intensity higher than 90 minutes. It should be noted, though, that in this trial the study arms differed both in counseling time and in pharmacotherapy use. In SST bupropion was prescribed to and used by all participants, while in the LMIS group 30% of patients used bupropion. Research shows that bupropion use increases quit rates among COPD patients [22], as it does in healthy smokers [23]. Furthermore, unlike the LMIS, the SST included group counseling, which tends to generate higher quit rates than individual counseling [e.g. 24]. This may also have contributed to the difference in effect rates. Although this may partly explain the difference in abstinence rate, it is likely that the more intensive counseling also contributed to a higher effectiveness, even at this level of intensity. However, as the specific intervention components were not compared separately in this study, a contribution of single components to effectiveness can only be assumed. In the SMOKE study, the design of the high-intensity smoking cessation program was based on existing recommendations from literature [9,11,16]. Our results thus support the validity of these recommendations. In our view, both the combination of multiple already proven elements, and the increased counseling intensity, have contributed to this outcome.

Smoking cessation is likely to lead to reduced costs for the health care payer in the longer term. The chosen follow-up period of 12 months in this study can therefore be considered as rather short. However, a recent systematic review considering the long-term effectiveness and cost-effectiveness of smoking cessation interventions for COPD patients confirms our short-term results [25]. They conclude that compared with usual care, intensive counseling and pharmacotherapy resulted in low costs per quality adjusted life years (QALY) gained with ratios comparable to results for smoking cessation in the general population. Additionally, the Lung Health Study demonstrated that COPD patients who quit smoking had an improvement in lung function in the first year, and a subsequent rate of decline that was half the rate observed among continued smokers [6]. As there is a strong association between COPD severity and use of healthcare services [e.g. 26,27], cost-savings are likely to occur in the first year of abstinence, as was shown by the present study.

In a similar vein, direct costs in this study consisted of exacerbations (including medication use) and hospitalizations following an exacerbation. The aim of the smoking cessation interventions was to slow down the progression of COPD symptoms. Smoking cessation can be assumed to reduce the number of exacerbations and consequently hospitalizations on the short term, based on the expected improvement in lung function after smoking cessation [e.g. 6]. Therefore, the focus was solely on disease-related exacerbations and hospital admissions. Furthermore, medication use for COPD other than for exacerbations, and hospitalizations due to other causes were assumed to be equal in both groups and not (largely) influenced by smoking cessation in the short time frame of 12 months.

This economic evaluation mainly aimed at providing information for decision makers. We took the viewpoint of the health care payer, who are the main decision makers in this context, to be able to promote the implementation of the smoking cessation intervention. However, an important disadvantage of this relatively narrow perspective is that is does not guard against cost-shifting, that is, where costs may decrease for one payer, they may rise for another. But aiming at secondary prevention of, for example, further and faster deterioration of COPD, this risk is considered to be small. And finally, it is likely that an analysis based on data administered from a societal viewpoint would result in the same conclusion, considering an earlier published cost-effectiveness analysis of antidepressants for smoking cessation in COPD patients [22].

Concerning the measurement of costs, a potential source of bias could have been that data on costs were collected by the pulmonary nurses, who were not blinded. Also, data were not collected continuously, but at baseline and at 12 months follow-up. To reduce the possibility of recall bias, frequent measurements of costs are generally preferred. In this study patients were asked to recall the number of exacerbations and hospitalizations in the previous 12 months. The number of hospitalizations is easy to recall as this occurs infrequently and has a strong impact. The reported number of exacerbations was validated with pharmacy records. The pharmacists of the patients were asked to provide information about the use of medication indicative of an exacerbation during the trial. Therefore, both a bias due to nurses' interference and a patient recall bias are unlikely to have affected the cost data of this trial.

Little is known about the effects of smoking cessation in COPD patients on mechanisms that may result in health benefits. Willemse et al. concluded in a review that respiratory symptoms, mental state and quality of life of COPD patients may improve after sustaining abstinence for one year [28]. However, they also concluded that airway inflammation increased and that smoking cessation may have induced such inflammatory response. The present study suggests an overall health gain as a result of smoking cessation, as a negative association was found between continuous abstinence on the one hand, and exacerbations and hospital days on the other hand.

To conclude, the results of the SMOKE study imply that, for COPD outpatients, a high-intensity counseling intervention with bupropion support may be preferred over a moderately intensive counseling intervention with only partial support of pharmacotherapy.

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4

Moving beyond a limited follow-up in cost-effectiveness analyses of behavioral interventions

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Abstract

Background. Cost-effectiveness analyses of behavioral interventions typically use a dichotomous outcome criterion. However, achieving behavioral change is a complex process in which several steps towards a change in behavior. Delayed effects may occur after an intervention period ends, which can lead to underestimation of these interventions. To account for such delayed effects, intermediate outcomes of behavioral change may be used in cost-effectiveness analyses. The aim of this study is to model cognitive parameters of behavioral change into a cost-effectiveness model of a behavioral intervention. *Methods*. The cost-effectiveness analysis (CEA) of an existing dataset from a RCT in which a high-intensity smoking cessation intervention was compared with a medium-intensity intervention, was re-analyzed by modeling the stages-of-change of the Transtheoretical Model of behavioral change. Probabilities were obtained from the dataset and literature and a sensitivity analysis was performed. *Results*. In the original CEA over the first 12 months, the high-intensity intervention dominated in approximately 58% of the cases. After modeling the cognitive parameters to a future second year of follow-up, this was the case in approximately 79%. *Conclusion*. This study showed that modeling of future behavioral change in CEA of a behavioral intervention further strengthened the results of the standard CEA. Ultimately, modeling future behavioral change could have important consequences for health policy development in general and the adoption of behavioral interventions in particular.

Introduction

Cost-effectiveness analyses (CEAs) in health care research and public health are considered an important tool to help decision-makers to set funding priorities [1,2]. CEA can be defined as the comparative analysis of alternative courses of action in terms of both their costs and consequences and is designed to improve health [3]. Exploring the cost-effectiveness of a *behavioral* health intervention, however, has some methodological implications compared to pharmaceutical interventions. Behavioral interventions encourage individuals to modify their existing behavior and to adopt a healthier behavior. CEAs of behavioral interventions typically use a simple dichotomous (success or failure) outcome criterion [4]. In reality, though, behavioral change is a complex process in which several steps towards success are taken. As most intervention studies have a relatively short follow-up period of six to 12 months, it is likely that effects are achieved after the follow-up period. In fact, any progress in behavioral change without accomplishing full behavioral change may also be considered as a beneficial outcome of the intervention [5]. Not accounting for 'delayed' behavioral change may lead to underestimation of effectiveness of behavioral interventions [6-9]. Obviously, extending the follow-up period would be the preferred way to address this issue. However, this is often impeded by practical and financial limitations. An alternative may be to use intermediate outcome measures to model future behavioral change. In their review on this topic, Wagner & Goldstein [4] stated that analysts who conduct a CEA of a behavioral intervention should not focus solely on people who successfully changed their behavior, but they also need to measure partial behavioral change. They conclude that failing to include partial behavioral change in the CEA can bias the results. Studies on interventions that collect stages of change data (e.g. Transtheoretical model of behavioral change [10]), for example, enable the measurement of partial behavioral change and the subsequent incorporation of these as intermediate outcomes into CEAs. Also non-stage-based psychological theories can provide measures of partial behavioral change, such as the Theory of Planned Behavior from Ajzen [11] and Bandura's Social Cognitive Theory [12].

The Transtheoretical model of behavioral change is a stage-oriented model that describes the readiness to change [13]. Beginning in 1977, Prochaska and colleagues developed the model, based on an analysis of different theories of psychotherapy. Nowadays, it has been widely adopted for numerous health behaviors [10]. A number of qualitatively different, discrete states, the 'stages-of-change', are key constructs of the Transtheoretical model. It provides an algorithm that distinguishes six stages; the focus of this study is on the first three 'pre-action' stages: 1) pre contemplation (e.g. no intention to quit smoking within the next six months); 2) contemplation (e.g. intending to quit smoking within the next six months); and 3) preparation (e.g. intending to quit smoking within the next 30 days) [10]. The stage algorithm has been developed on the basis of empirical findings [14]. These pre-action stages provide probabilities for the *actual* transition to the fourth stage, the 'action stage' in which full behavioral change is achieved. The other two stages are the 'maintenance stage' (in which people changed their behavior more than six months ago) and the 'termination stage' (in which people have achieved maintenance and no longer experience any temptations and have full self-control; people may never enter this stage). Usually, attempts to modify (addictive) behavior are not immediately successful. With smoking, for example, successful quitters make an average of three to four attempts and go through a spiral pattern of several cycles before they reach long term abstinence. Relapse and recycling through the stages therefore occur quite frequently as individuals attempt to modify or cease addictive behaviors [10].

Modeling of partial to future behavioral change has previously been applied in CEA literature. For example, Tengs et al. created the 'Tobacco Policy Model' to estimate cost-effectiveness of school-based anti-tobacco education over one's life-time [15]. They defined and simulated successfully three changes in smoking behavior using a Markovian computer simulation model: The transition from never smoked to being a current smoker (initiation), from current to former smoker (cessation) and from former to current smoker (relapse). Also for public health modeling, Mulder et al. applied changes in smoking status to predict future mortality reduction through smoking cessation [16]. These are *behavioral* intermediate outcomes. An alternative may be to use *cognitive* parameters. Cognitive parameters are the antecedents of actual behavioral change, as reported in several behavioral theories in literature (e.g. Transtheoretical model [13], Theory of Planned Behavior [11]).

The aim of this study is to model cognitive parameters into the final cost-effectiveness model of a behavioral intervention to gain more insight into the feasibility and the challenges involved with this method. For this purpose we used an existing dataset and replicated the CEA with addition of partial behavioral change estimates, based on the stages-of-change algorithm.

Methods

Sample

Data from the SMOKE study [17,18] were used. The SMOKE study is a randomized controlled multi-centre trial with one year follow-up which evaluated the (cost-) effectiveness of the SmokeStopTherapy (SST) and the Minimal Intervention Strategy for Lung patients (LMIS). A total of 234 COPD patients motivated to quit smoking (checked by their own chest physician) were included in the SMOKE study and randomly assigned: 117 received the LMIS and 117 patients received the SST. Inclusion criteria were clinically diagnosed moderate COPD (% predicted FEV1=50-69) or severe COPD (% predicted FEV1<50 as defined by the American Thoracic Society (ATS) criteria [19], willingness to participate in a smoking cessation program, aged between 40 and 75 years, and adequate knowledge and understanding of the Dutch language. The only exclusion criterion was a counter indication for the use of Bupropion (Zyban®). The chest physician advised each smoking COPD patient to quit smoking and, after providing informed consent, the patients was referred to the SMOKE study. A total of nine patients dropped out after giving informed consent: six from the LMIS and three from the SST. At baseline, another 15 patients dropped out: six from the LMIS and nine from the SST. They were excluded from all analyses. In both conditions 105 patients remained for analyses. All missing patients at 12 months follow-up were assumed to be smokers. All remaining patients adhered to the counseling sessions.

Baseline characteristics are presented in Table 1. Three baseline differences were found between groups. Patients receiving LMIS were older than those receiving the SST ($p<.05$). Nicotine dependence, as measured by the Fagerström questionnaire, was significantly stronger in the participants allocated to the SST compared to LMIS ($p<.05$). In relation to this finding, the nicotine addiction, as indicated by the categorical outcome of the Fagerström questionnaire, was also stronger in the SST compared to the LMIS ($p<.01$). In a previously published prospective analysis of predictors of quitting in this sample [18], these three baseline characteristics appeared not to be predictive of validated abstinence at 12 months follow-up. A bias due to these baseline differences is therefore unlikely.

Table 1. Baseline characteristics of 225 outpatients with COPD

Variables	Minimal Intervention Strategy for Lung patients (n=111)	SmokeStopTherapy (n=114)
Gender, Male / Female	63 (57%) / 48 (43%)	55 (48%) / 59 (52%)
Age, yr*	59.6 (8.51)	57.0 (8.41)
FEV_1, L	1.86 (.85)	1.93 (.91)
FEV_1 % predicted of normal	62.8 (25.7)	65.6 (27.4)
IVC, L	4.78 (8.45)	4.71 (7.88)
Cotinine value, ng/ml	292 (144)	324 (145)
Cigarettes daily	20.5 (13.5)	24.1 (13.8)
Pack-years	41.7 (23.9)	46.4 (25.4)
Previous quit attempts (>24hr)	2.89 (5.95)	2.47 (3.38)
Quality of life (SGRQ) three domains, range 0-100		
Symptoms	52.2 (22.4)	51.4 (22.9)
Activity	55.6 (22.5)	54.6 (23.4)
Impacts	28.6 (16.8)	32.7 (19.8)
Total	40.7 (16.7)	42.5 (19.1)
Depression (BDI), range 0-63	12.1 (8.45)	9.84 (8.37)
Nicotine dependence (Fagerström), range 0-10**	4.98 (2.05)	5.84 (2.14)
Nicotine addiction (Fagerström score ≥6), Yes / No*	39 (42%) / 54 (58%)	58 (59%) / 40 (41%)
Education level		
High	20 (19%)	13 (13%)
Middle	32 (30%)	30 (31%)
Low	54 (51%)	54 (56%)

Note. *p<.05, **p<.01. Characteristics are presented as means (standard deviation) or numbers (%).

SMOKE study

The SMOKE study compares two smoking cessation interventions: the medium-intensity program LMIS and the high-intensity program SST in a COPD outpatient setting. The SST is a multi-component smoking cessation intervention that consists of group counseling, individual counseling and telephone contacts, supported by the obligatory use of Zyban®, free of charge. The SST provides the possibility to repeat the individual sessions after experiencing a lapse within three months. The LMIS is an existing Dutch intervention that is considered as current practice for smoking lung patients in the Netherlands [17]. This intervention consists of individual counseling and telephone contacts. Pharmacological support is recommended during LMIS counseling, but use is voluntary and at the patients' cost. The SMOKE study [17] showed the SST to be cost-effective compared to the LMIS, expressed as cotinine-validated continuous abstinence rates after one year. The number of quitters was 20 in the SST versus nine in the LMIS and the associated costs were €3,101 per quitter in the SST and €6,832 per quitter in the LMIS. The SST had dominancy over the LMIS on each outcome parameter in the first 12 months; the SST showed higher effects and lower costs [17].

Economic evaluation

Decision trees were used to outline the cognitive states and the pathways a COPD patient could experience, over the time frame of 12 to 24 months. They were used to calculate future behavioral change, the associated costs, and subsequently the incremental cost-effectiveness of the SST over the LMIS. Table 2 shows the base case probabilities with the associated 95% confidence intervals (CI). They illustrate the pathways a COPD patient could experience for each arm in the decision tree based on data from the SMOKE study. The primary outcomes are the expected costs of both interventions per quitter.

Table 2. Base case values of the probabilities in the decision tree for LMIS and SST for the continuous abstinence outcome measure

LMIS (n=105)	n	Base case values *(95% CI)*
CA	9	.086 (.032-.14)
CA + Exa	5	.556 (.225-.887)
CA + Exa + Hosp	0	.000*
CA + Exa + no Hosp	5	1.000**
CA + no Exa	4	.444 (.113-.775)
CA + no Exa + Hosp	0	.000*
CA + no Exa + no Hosp	4	1.000**
No CA	96	.914 (.86-.968)
No CA + Exa	46	.479 (.377-.581)
No CA + Exa + Hosp	10	.217 (.095-.339)
No CA + Exa + no Hosp	36	.783 (.661-.905)
No CA + no Exa	50	.521 (.419-.623)
No CA + no Exa + Hosp	0	.000*
No CA + no Exa + no Hosp	50	1.000**
SST (n=105)		
CA	20	.19 (.113-.267)
CA + Exa	12	.600 (.381-.819)
CA + Exa + Hosp	1	.083 (.000-.242)
CA + Exa + no Hosp	11	.917 (.758-.999)
CA + no Exa	8	.400 (.181-.619)
CA + no Exa + Hosp	0	.000*
CA + no Exa + no Hosp	8	1.000**
No CA	85	.81 (.733-.887)
No CA + Exa	29	.341 (.238-.444)
No CA + Exa + Hosp	4	.138 (.01-.266)
No CA + Exa + no Hosp	25	.862 (.734-.99)
No CA + no Exa	56	.659 (.556-.762)
No CA + no Exa + Hosp	0	.000*
No CA + no Exa + no Hosp	56	1.000**

Note. CA = Continuous Abstinence; n = number of participants in each arm; *95% CI* = 95% Confidence Interval; Exa = Exacerbation; Hosp = Hospital admissions; LMIS = Minimal Intervention Strategy for Lung patients; SST = SmokeStopTherapy; *The assumption was made that for the actual point values of 0, the point value was .0025; ** The assumption was made that for actual point values of 1, the point value was .95

Additionally, probabilities were extracted from the data to determine the *distribution* in stages-of-change for the smokers at 12 months. Participants who were abstinent at 12 months were all automatically assigned to the ‘action stage’, regardless of the duration of their non-smoking status. For several reasons the ‘maintenance’ and ‘termination’ stages were not distinguished separately. First, the time horizon of the model is limited to 12 to 24 months. Second, this makes the model more parsimonious and transparent. Third, differentiating the subjects to more than four groups would further increase the confidence intervals of the probabilities and this would lower the statistical power with the limited sample size. Participants who reported to be smokers at 12 months filled in a standardized stage-of-change questionnaire [20]. Of the smokers in the LMIS, 30.6% (*95% CI*: 15.6–45.7) were in the pre contemplation stage, 44.4% (*95% CI*: 28.2–60.6) were in the contemplation stage and 25% (*95% CI*: 10.9–39.1) were in the preparation stage of behavioral change. For the SST these probabilities were respectively 27.8% (*95% CI*: 13.2–2.4), 38.9% (*95% CI:* 23.0–54.8), and 33.3% (*95% CI*: 17.9–48.7), respectively.

Probabilities TTM – weighted average

To predict future behavioral change by the stages-of-change as cognitive parameters, probabilities for the *transition* from the first three ‘pre-action’ stages-of-change to the action stage (in which the actual desired behavior is performed) were collected from literature. The preferred time frame for these probabilities is 12 to 24 months. A thorough search of the electronic databases indicated that there are no transition probabilities available for smoking COPD patients in this specific time frame. Therefore, a weighted average was used of multiple transition probabilities reported in literature. Included were transition probabilities of smoking cessation interventions, among different populations, interventions and outcome measures. Studies among adolescents were excluded to limit heterogeneity. The formula used for calculating the weighted average with numbers $x_1.....x_n$ and weights $g_1.....g_n$ was:

$$\bar{x} = \frac{\sum_{i=1}^{n} g_i x_i}{\sum_{i=1}^{n} g_i}$$

Table 3 shows the characteristics and probabilities of the included studies.

Table 3. Characteristics of included studies for the weighted average of transition probabilities stages-of-change (Transtheoretical model) for 12–24 months

Author	*Inter vention*	*Popu lation*	*N*	*Time horizon*	*Out come measure*	*Pre contem plation*	*Contem plation*	*Prepa ration*
Carbonari [42]	Minimal	General smokers	308	12 – 18	PP	.130	.064	.070
Carbonari [42]	Minimal	General smokers	308	18 – 24	PP	.020	.058	.016
Carbonari [42]	Minimal	General smokers	308	6 – 12	PP	.100	.093	.118
Carbonari [42]	Minimal	General smokers	308	Time + 1	PP	.064	.084	.115
DiClemente [43]	Minimal	General smokers	1466	0 – 6	PP	.079	.118	.208
Schumann [50]	Stage based	General smokers	240	0 – 12	PP	.029	.013	.004
Schumann [49]	No	General smokers	786	0 – 6	PP	.024	.100	.100
Hilberink [45]	Yes	COPD	244	0 – 6	PP	.134	.167	.206
Hilberink [45]	No	COPD	148	0 – 6	PP	.080	.071	.154
Hilberink [48]	Yes	COPD	243	0 – 12	PP	.082	.078	.111
Hilberink [48]	No	COPD	148	0 - 12	PP	.027	NA	.115
Hilberink [48]	Yes	COPD	243	0 - 12	PA	.010	.038	.048

(continues)

Table 3. Characteristics of included studies for the weighted average of transition probabilities stages-of-change (Transtheoretical model) for 12–24 months **(continued)**

Author	*Inter vention*	*Popu lation*	*N*	*Time horizon*	*Out come measure*	*Pre contem plation*	*Contem plation*	*Prepa ration*
Hilberink [48]	None	COPD	148	0 - 12	PA	.013	NA	.077
Hilberink [48]	Yes	COPD	243	0 – 12	CA	.010	.038	.032
Hilberink [48]	No	COPD	148	0 – 12	CA	.013	NA	.038
Hennrikus [46]	Yes	Smoking workers	802	0 – 24	PA	.020	.060	.110
Farkas [47]	No	Current smokers	818	0 – 24	PP	.070	.080	.110
Callaghan [44]	Yes	General smokers	25	0 – 12	PP	.030	.040	NA

Note. PP = Point Prevalence, PA = Prolonged Abstinence, CA = Continuous Abstinence, COPD = Chronic Obstructive Pulmonary Disease, NA = Not Applicable.

Relapse rate

Delayed negative effects of behavioral interventions should be taken into account as well: individuals who relapse in their old (smoking) behavior after they had reached successful behavioral change. An annual relapse rate of 10% (*95% CI:* 5-17) for the time frame 12–24 months was obtained from Hughes et al. [21]. They conducted a meta-analysis of prospective studies of adult quitters that reported the number of participants abstinent at one year follow-up and who remained abstinent at ≥two years follow-up (prolonged abstinence). In retrospective datasets of non-treatment samples, among those abstinent at one year, 2–15% relapsed each year thereafter. The meta-analysis estimated the incidence of relapse to be 10% per year.

Costs

Costs were based on the costs of the SMOKE study for the first 12 months follow-up. They were calculated following a health care perspective, previously reported by Christenhusz et al. [17]. For 12 to 24 months follow-up, intervention costs were set to 0. Costs regarding exacerbations (€101.25) and hospitalizations (€3,140) were included in the analysis. Because of the different time frames associated with each stage-of-change, we calculated costs per stage-of-change. For example, the Transtheoretical Model assumes that a smoker in the 'preparation' stage will quit within one month. Consequently, this individual will be run through the model as a smoker during one month and 11 months as a quitter. Following this procedure, all costs in the cost-effectiveness model were adjusted for the different stages-of-change the participants were in after 12 months follow-up. Costs and effects were not discounted for time preference.

Figure 1 shows the distribution in smoking status and cognitive states after 12 months of follow-up, the relapse rates for the second year, the weighted averages for prediction of future behavioral change and their associated costs for the SmokeStopTherapy.

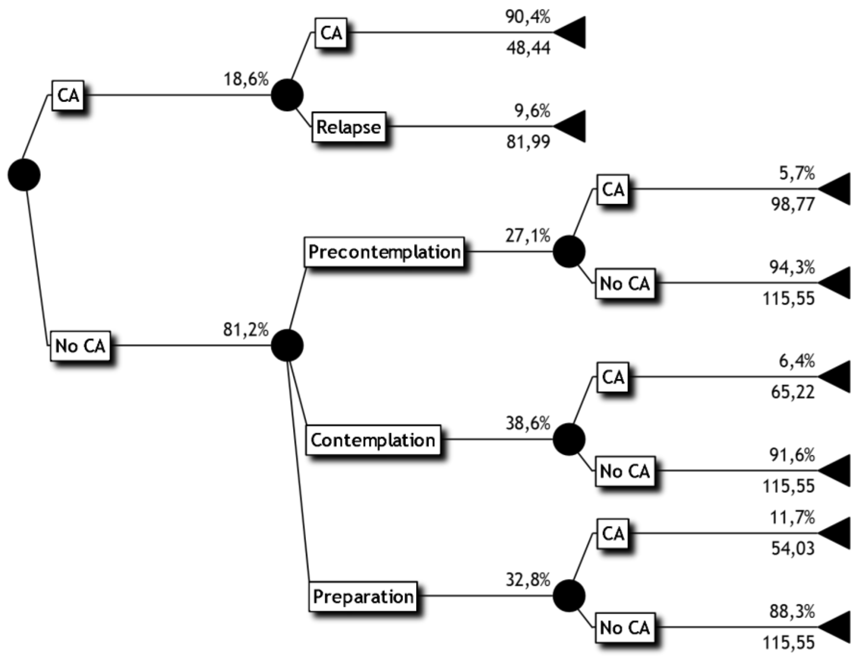

Figure 1. Pathways for the continuous abstinent (CA) and not continuous abstinent arm (No CA) of the SmokeStopTherapy (SST) for the time frame 12-24 months, including percentages and costs (€)

Sensitivity analyses

All variables were evaluated for uncertainty into the sensitivity analysis. Uncertainty regarding data inputs was quantified by means of a Monte Carlo simulation with 1,000 iterations to explore the variation of the total costs as well as the costs per quitter, and the amount of quitters by varying the cost parameters and probabilities simultaneously over their ranges and the associated 95% confidence intervals. A gamma distribution was assumed for all costs and a logistic normal distribution for all probabilities. Sensitivity analyses were performed using @Risk 5.5 for Excel (Palisade Corporation, 2010).

Results

The total costs of an average COPD patient within the SST for the second year (12–24 months follow-up) was €99 compared to €301 for the LMIS. The costs generated by subjects of the SST were considerably lower and the SST achieved a larger amount of quitters compared to the LMIS. Costs per quitter generated by the subjects for the LMIS were €2,047 and €413 for the SST. The SST had dominancy over the LMIS on each outcome parameter over the first 12 months, and results also show dominancy over 12 to 24 months.

The weighted averages of the transition probabilities for the three pre-action stages of change to the action stage for 12-24 months were: .059 (*95% CI:* .035-.082) for 'pre contemplation', .085 (*95% CI:* .059-.111) for 'contemplation' and .118 (*95% CI*: .087-.149) for the 'preparation' stage. Over the period from baseline to 24 months, 25 patients in the SST quit smoking versus 15 patients in the LMIS, which indicated a slightly lower difference in effect between both interventions, compared to the first 12 months. The total costs per quitter, after accounting for a 10% relapse rate, were respectively €3,514 and €8,879, with a difference of €5,365 in favor of the SST. Analyses for the point prevalence outcome measure showed similar outcomes.

Sensitivity analysis of the decision analytic model

Probabilistic sensitivity analysis was employed to analyze the robustness of the above mentioned findings. The estimates of costs and effects for both the original SMOKE study and this pilot study are graphically represented in Figure 2.

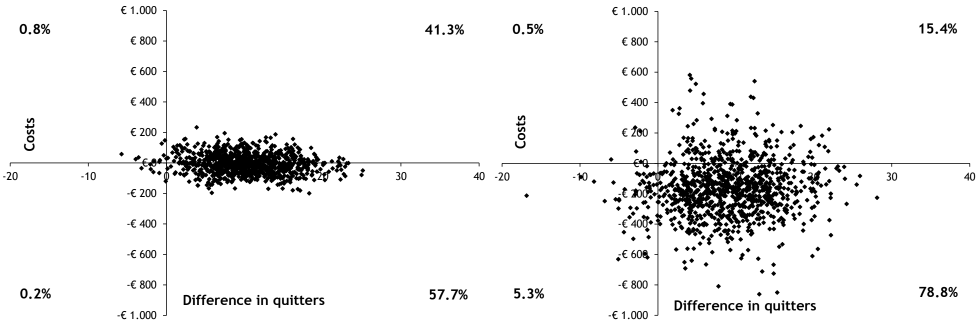

Figure 2. Monte Carlo simulation results for costs per additional quitter, period 0–12 months (left) and 12–24 months (right). A negative € amount and a positive difference in number of quitters favor the SST. Percentages of simulations in each quadrant are given

Figure 2 represents the difference in costs associated with the difference in number of quitters. In almost all iterations a higher number of quitters is associated with the SST. In the original SMOKE study (0–12 months; Figure 2 (left)), the observed costs were in approximately 58% of the iterations lower for the SST than for the LMIS [17]. This rate increased to 84.1% of iterations in favor of SST in the data generated for 12-24 months in this pilot study (Figure 2 (right). After simulation, the mean difference in number of quitters at two years is 8.95 (*95% CI*: -0.95–18.84), favoring the SST. The mean difference in total costs between both interventions is €165.21 (*95% CI*: -450.73–150.15) and the mean difference in costs per quitter is €1,505.57 (*95% CI*: -3424.20–74.15), also in favor of the SST. Almost 79% of the iterations are in the south eastern quadrant of the cost-effectiveness plane, which indicates the SST to be dominant over the LMIS for the time frame 12-24 months.

Discussion

Data from the SMOKE study [17] were used to re-analyze a CEA with addition of partial behavioral change estimates based on the stages-of-change algorithm. In the time frame of 12–24 months, the high-intensity smoking cessation intervention for COPD patients (SST) is more effective and less costly in approximately 79% of all simulations compared to 58% of the simulations in the first year. Thus, the SST dominates the medium-intensity smoking cessation intervention (LMIS) even more in this future second year of follow-up with inclusion of partial behavioral change.

The present paper illustrates a way to integrate psychological theories into the methodology of health economic evaluations. As the cost of health care rises and consequently CEAs become more important, decision makers have to be optimally informed about the cost-effectiveness of different treatment options [22]. Interventions that aim to accomplish behavioral change can have delayed effects that may influence the cost-effectiveness results [23-25]. This suggests that the commonly applied follow-up period of 12 months may not be sufficient to reflect the true, longer term outcomes. Modeling of partial behavioral change could serve as an alternative way to include future effects into the cost-effectiveness ratio. Smith et al. [26] already reported a way to incorporate future effects by modeling the cognitive 'pre-action' stages-of-change. They included partial behavioral change in their CEA of a computer-based smoking cessation intervention in primary care by advancing a smoker's stage-of-change. However, no transition probabilities or validation of their methods were reported. In the present study, we intended to make the steps that are necessary to model partial behavioral change more transparent. Consequently, this revealed some of the methodological and empirical issues that need to be addressed to further validate this approach.

One of these issues is the predictability of the modeled cognitive parameters. Obviously, one prerequisite is a high and empirically supported predictive value of these parameters. Concerning the Transtheoretical model, there is some debate about the validity of the model in literature. Proponents have argued that application of the model has revolutionized health promotion, but others have suggested that the problems with the model are so serious that it has held back advances in the field of health promotion and, despite its intuitive appeal to many practitioners, it should be discarded [27]. However, critique and debate on the Transtheoretical model is mainly focused on its supposed usefulness for designing stage-based, tailored interventions with superior effectiveness [28-30]. It is the predictive validity of the stages itself that has received strong empirical support; people who are further along the continuum are more likely to change their behavior at a future follow-up point than those who are at an earlier stage [31,32]. In literature about the model, these stage effects appear to be highly consistent [33]. Nevertheless, some care needs to be taken as our study showed a considerable variability in transition probabilities reported in literature (Table 3).

Considering this, is the cure worse than the disease? Health economic evaluations in general are vulnerable to manipulation due to the use of primary data and the arbitrary definition of outcomes. The definition of meaningful outcome parameters is a precondition for the validity of a study. These endpoints should be clearly relevant in relation to health improvement. Predicting full behavioral change after the intervention period ends, and thus substituting a missing endpoint, may increase uncertainty compared to using an observed outcome parameter like, in this case, smoking cessation. However, uncertainty is pervasive in CEAs [34] and this is generally accepted. Also, developments in health behavior research are promising. More and more evidence becomes available from theory-based psychological research to determine the uncertainty that comes with predicting full behavioral change using cognitive parameters. This applies to both smoking cessation and other health behaviors. Additionally, the aim was to show the feasibility and challenges of incorporating cognitive intermediate outcomes into CEAs of behavioral interventions. Therefore, no issues regarding discount rates, time dependency and Markov modeling were taken into account, which would probably result in more exact estimates of outcomes and reduce uncertainty.

As partial behavioral changes based on the stage effects of the Transtheoretical model can be incorporated in economic evaluations, this may also be valid for other models of behavioral change [4], such as Ajzen's Theory of Planned Behavior [35,36] for which ample empirical support is available. However, this may require other modeling techniques, like discrete event simulation, as this theory provides a multidimensional continuum, and no discrete Markov states.

In this study the focus was not on the health effects on the long term, but rather on reducing the risk factor that exacerbates the disease. For decision makers, though, future health benefits and costs are more informative than the costs per quitter following the intervention. The presented method in this article could therefore serve as an extension or antecedent of several predictive models for COPD reported in literature [37-39], in which disease progression and death are predicted based on, among others, smoking status.

Quit rates following smoking cessation interventions have shown to be rather disappointing for the COPD population. These patients tend to have a long smoking history, a long history of failed quitting attempts, and a very strong nicotine addiction [40,41]. However, transition probabilities for the pre-action to the action stage-of-change (TTM) seem not be very different between populations. Table 3 shows similar probabilities for transitions for COPD patients and the general population. Therefore, applying the method presented in this paper to a CEA of an intervention among the general population, will likely show similar effects.

In conclusion, the results indicate that modeling of future behavioral change in a CEA of a behavioral intervention in general may lead to a change in results. As the intervention in the present study was already dominant over the first year and merely became more dominant over the second year, though, the observed change in results would not have led to another decision. In this case the standard CEA would have been sufficient for decision makers. However, in many cases an ICER may turn out to be less favorable or may approach or even exceed the threshold of willingness to pay. Under such conditions, including partial behavioral change in the CEA could have a decisive impact. Furthermore, effectiveness data from existing behavioral interventions that were not assessed with the purpose of conducting a CEA, are often unsuitable for CEAs due to variation in the length of follow-up or due to a lack of adequate behavioral endpoints. Modeling of cognitive parameters of behavioral change may provide a way to overcome such variations between studies, by estimating the required behavioral endpoints for use in CEAs. Ultimately, modeling future behavioral change can have important consequences for public health policy development in general and the adoption of behavioral interventions in particular.

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5

Cognitive covariates of smoking cessation: Time-varying versus baseline analysis

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Abstract

Background. Behavior change is a gradual process including cognitive changes in the course of time. Prediction analyses of behavior change using cognitive parameters are usually limited to measures at single points in time, or use daily measures, limiting its practical applicability. The present study examined the time-varying nature of the psychological covariates that result in smoking abstinence in commonly used follow-up periods. Two main issues are addressed: the time-varying nature of the outcome and the time-varying nature of the covariates. *Methods*. Data were used from the SMOKE study in which two smoking cessation interventions were compared for COPD outpatients. The covariates self-efficacy, social support, attitude and descriptive norm were measured at baseline, six and 12 months of follow-up. Two different Cox models were estimated: 1) time-varying covariates predicting abstinence at six and 12 months and 2) single-point covariates predicting abstinence for fixed time periods. *Results*. Self-efficacy appeared to be the major indicator of smoking cessation in a time-varying analysis (R^2= 20.5%), with a bidirectional causal relation to the outcome. In contrast, attitude and descriptive norm were weak significant baseline predictors for smoking abstinence. *Conclusion*. This study underlined the distinction of baseline versus time-varying analyses, as the reciprocal association of self-efficacy during the course of one year with actual behavior change. Time-varying Cox analyses are a valid and feasible approach to reflect indicators of the behavior change process. Results are in line with literature and suggest a high practical applicability as underlying covariates of behavior change are captured using commonly used follow-up periods.

Introduction

Social cognitive theories provide constructs that have shown to be predictive of multiple health behaviors [1], such as smoking cessation. In many smoking cessation studies predictor variables are based on stable individual differences. These ratings are used to predict who will and who will not abstain from smoking at some future time point. However, these predictor variables may change over time [e.g. 2-4]. Also, it should be recognized that people tend to cycle between smoking and abstinence before reaching a steady state [5,6]. For the purpose of predicting outcomes of the complex and fluctuating process of behavior change, it seems more appropriate to use a time-varying approach. Overall, two main issues are addressed here: firstly the time-varying nature of the outcome (behavior), and secondly the time-varying nature of the social cognitive predictors.

Studies have shown that 80 to 90% of those who naturally quit smoking will likely relapse within three months [7]. However, short relapses may be followed by renewed quit attempts relatively quickly [8]. Thus, quitting behavior is not so much characterized by a final end state of relapse or abstinence, but rather by a sequence of smoking and non-smoking states that can occur over relatively short intervals [9]. Therefore, it may not be valid to solely focus on the end point to be predicted if fluctuations of smoking status within individuals at other time points exist. This does not address the complex process that may occur during smokers' attempts to quit and remain abstinent [e.g. 10]. Thus, important questions will remain regarding the working mechanisms for those events.

Psychological constructs, such as self-efficacy, are associated with the processes of smoking cessation and (re)lapses [e.g. 2,11-13]. Multiple studies have shown that patterns of social cognitive variables change before and after a quit attempt or relapse [3,4,14]. For example in the Social Cognitive Theory, self-efficacy is a central construct which is defined as the conviction that one can successfully execute the behavior required to produce the desired outcomes [11]. Also, the Theory of Planned Behavior (TPB) [15] has been applied to predict smoking cessation successfully [16]. According to TPB, smokers with a positive attitude towards smoking cessation, a high perceived behavioral control to refrain from smoking, and a high perceived social pressure to stop smoking will have a stronger intention to accomplish the desired behavior. In the current study, behavioral determinants embedded in the ASE model were examined [17]. The ASE model originated in the Theory of Reasoned Action [18] and the Social Cognitive Theory of Bandura [11,19]. It postulates that behavior can be explained by behavioral intention, which in turn is determined by attitudes, perceived social influences and self-efficacy expectations. Social influences can be divided in three distinctive constructs: social support and encouragement from a person's social environment to refrain from smoking, the perceived subjective norm from others and the descriptive norm, meaning the perceived behavior of others. Social cognitive models suggest that cognitive variables change over time in response to changing internal and external contexts and challenges and that this variation is causally related to smoking cessation and (re)lapses [12].

On the other hand, multiple studies have found a reciprocal relation between cognitions and behavior change. For example, self-efficacy changes when measured post-treatment and a decrease in self-efficacy among abstinent smokers is predictive of future relapse [e.g. 20,21]. Additionally, a study examining daily measures of self-efficacy in relation to lapses and relapses found that self-efficacy was insensitive to events before a lapse, but is sensitive to the lapse itself [2]. Furthermore, current evidence-based behavioral interventions generally are designed on the basis of such social cognitive models and are assumed to promote behavior change through beneficial changes in these psychological processes [22]. Thus, to be able to analyze changes in processes over time, a time-varying approach seems promising.

In the present study the data of the SMOKE study were re-analyzed in a time-varying analysis [23]. In a previous study, Christenhusz et al. [23] examined the baseline characteristics of smoking COPD patients participating in a smoking cessation program (SMOKE study), that predict successful quitting. Of the psychological covariates studied in this model, only attitude towards quitting appeared to contribute significantly to the prediction of continuous smoking abstinence at 12 months follow-up. This finding was in line with earlier studies [e.g. 24], but seems to lack important information of underlying working mechanisms over time, as for example, an influential and time-varying role of self-efficacy has been indicated in multiple studies [e.g. 2,3,25].

Several analytic techniques are available for analyzing the working mechanisms of trials in tobacco treatment [26]. Hall et al. [26] make a distinction between 'time-naïve methods' en 'longitudinal designs'. The major advantages of longitudinal methods over time-naïve methods are 1) the effects of time can be estimated and tested directly, 2) one can accommodate both time-invariant and time-varying covariates and finally, they allow model estimates based on all available data. Examples are Generalized Estimating Equations (GEE), Generalized Linear Mixed Models (GLMM) and Cox regression analysis with time-varying covariates. The aim of the current study is to examine multiple measurements including data on cognitions, but also outcome measure. Cox regression analyses with time-varying covariates were applied in this study, as its design can be modified to handle recurrent events (e.g. a person can quit smoking and relapse). For tobacco relating trials this technique has been previously applied for analyzing relapse [e.g. 27,28]. Advantages are that first, it can be applied to analyze multiple follow-up periods. Second, it handles censored cases. A case is censored if an event of interest is not recorded. Third, the analyses do not require a normally distributed dependent variable (such as a binary smoking status) and finally, it is a multivariate model [27].

In the current study Cox regression methods with time-varying covariates were applied to examine the contribution of social cognitive covariates to smoking cessation including multiple follow-up periods.

Methods

SMOKE study

Our study used data from the SMOKE study in which two smoking cessation interventions, specifically designed for smoking outpatients with COPD, were compared. A sample of 234 eligible smoking patients with COPD ranging in age from 40 to 75 with moderate to severe COPD was randomly allocated to a high-intensity intervention (595 minutes of total counseling time) called the SmokeStopTherapy (SST) or a moderately intensive intervention (180 minutes), the Minimal Intervention Strategy for Lung patients (LMIS). Both interventions have a course of three months. The SST is a multi-component smoking cessation intervention with small-group counseling, individual counseling and telephone contacts, supported by prescribed use of Zyban® and a possibility to repeat the individual sessions after experiencing a lapse within three months. The LMIS is a less intensive intervention containing individual counseling and telephone contacts. It is an existing Dutch intervention, currently available in most pulmonary outpatient clinics in Dutch hospitals. Pharmacological support is recommended during LMIS counseling, but use is voluntary. The sessions of the LMIS are less intensive and take place at a lower frequency compared to the SST. Both interventions are described in more detail elsewhere [23]. A total of nine participants dropped out after informed consent: six from the LMIS and three from the SST. At baseline, another five participants dropped out from the SST. They were excluded from all analyses. A total of 109 patients in the SST and 111 patients in the LMIS remained for analyses. All missing patients at follow-up were assumed to be smokers. The validated continuous abstinence rate (using salivary cotinine) one year after the start of the intervention was used as the primary outcome measure. Based on this criterion the SST was found to be more effective than the LMIS (continuous abstinence is 19% (SST) versus 9% (LMIS); *RR*=2.22; *95% CI*: 1.06-4.65) [23].

Measurements

Measurements took place at baseline and at six and 12 months follow-up. The outcome variable in the current study is point prevalence abstinence from smoking, which is defined as abstinence for the past seven days at a specific point in time. When patients reported abstinence at six or 12 months follow-up, a salivary sample was collected for cotinine assessment by means of a Salivette (Sarstedt AG & Co., Nümbrecht, Germany). The full procedure is described elsewhere [29]. Validated point prevalence quit rates were 20.9% at six and 16.4% at 12 months.

Proposed predictors of smoking cessation were drawn from established psychosocial models of health behavior [15,17] and have been used in past research exploring predictors of quitting. For measuring the psychosocial constructs (self-efficacy, descriptive norm, attitude and social support) the Smoking Related Questionnaire from Mudde et al. [30] was used, which scales were validated in earlier studies [e.g. 31]. A higher score on attitude reflects a more positive attitude towards smoking cessation. For self-efficacy, higher scores on the construct imply more confidence in being able to refrain from smoking in high-risk situations. Similarly, higher scores on social support are associated with greater support and encouragement from a person's social environment to refrain from smoking. For descriptive norm low scores indicate that most (or all) relatives and friends are non-smokers, which is supposed to facilitate quit attempts. Responses to each item were recorded on 4- or 5-point Likert scales.

Analyses

Cox proportional hazard models with time-varying covariates were fit to test the longitudinal relationship between potential covariates and smoking abstinence over the study period of one year using its predefined measurements at baseline, six and 12 months of follow-up. This produces a time-varying survival model that reports covariate effects as a hazard ratio, also called relative risks. The hazard ratios are based on the combined follow-up data. It is presumed that the log hazard ratio is additively related to the covariates by the linear predictor [32]. This leads to the assumption of proportional hazards (PH assumption), which implies that the ratio of two hazards (the relative risk) is independent of time [32,33]. However, this is doubtful in numerous situations, as for example a treatment effect may vanish over time or the impact of a covariate may react with some delay. To describe the dynamic development of the relative risk, the Cox PH model can be modified to a dynamic Cox model by allowing the effects to vary with time [32]. A time-varying covariate is defined as any variable whose value for a given subject may differ over time.

For the Cox models survival libraries implemented in R packages were used [33]. All four cognitive variables were included in the models as main effects. Potential for collinearity problems between the observed covariates was assessed with bivariate correlation analyses using Predictive Analytics SoftWare (PASW) Statistics 17. The PH assumption was examined by correlating the corresponding set of scaled Schoenfeld residuals with a suitable transformation of time, based on the Kaplan-Meier estimate of the survival function [33].

Two different kinds of Cox models were estimated in this study. Firstly, a Cox model with time-varying covariates was estimated using two validated point prevalence abstinence measures at six and 12 months and covariates at baseline and six months follow-up. Additionally, this same model was re-fitted to the data, but now using mean values for the four covariates to be able to incorporate values of all three measurement in the analyses. Mean covariate values for the period from baseline to six months and from six to 12 months follow-up were calculated to examine its relation to smoking cessation at six and 12 months follow-up.

Furthermore, single or fixed time periods were examined by means of Cox models. First, a Cox model was fit using baseline covariates to predict smoking cessation at 12 months follow-up. This allowed us to re-analyze the prospective prediction analyses by means of a logistic regression model [23]. Second, to further explore the underlying mechanisms of the time-varying model, Cox models were fit to the data using baseline covariate values to predict smoking abstinence at six months follow-up and six months covariate values to predict smoking abstinence at 12 months follow-up.

The outcome of interest is a dichotomous variable classifying subjects as abstainers or smokers. The Cox model analyses different time *periods,* which were characterized by the start- and endpoint between two measurements. Therefore, the lag time for each time period was six months. As participants could quit smoking and relapse in the same intervention period, subjects that reached the event of abstinence should not automatically leave the model as in regular survival analysis, but continue the process of quitting after cessation. Therefore, it is necessary that each time period for an individual appears as a separate observation. Additionally, we adjusted for the fact that the time periods within one patient are dependent [33]. Because data consist of multiple observations per subject, the robust variance estimate was used to account for the repeated observations of each subject [33,34].

A backward elimination procedure was applied to remove covariates from the Cox models which did not appear to contribute significantly to the outcome. These variables were eliminated individually until parameter estimates for all remaining variables were associated with *p*-values of less than .05.

Results

Baseline characteristics and smoking cessation

Population characteristics for all participants are presented here briefly, as are the baseline characteristics for the present sample (Table 1). One-year validated point prevalence rates in the total sample were 16.4% (36/220); 12% (13/111) for the Minimal Intervention Strategy for Lung patients (LMIS) and 21% (23/109) for the SmokeStopTherapy (SST). The option to recycle was used by 20% (22/109) of the participants in the SST group. None of these participants reached abstinence from smoking at 12 months after the start of the intervention. Compliance with assessment taking was low – participants completed an average of 55% of all three assessments. Information at baseline and both follow-up measurement was available for 99 participants (45% of enrolled patients) applying complete case analysis. For both the fixed and time-varying models this *same* group of patients was analyzed for reasons of comparability. As the two time periods were analyzed separately, this resulted in 198 cases. For the present sample (*n*=99), validated point prevalence quit rates were 34.3% and 26.3% respectively for six and 12 months follow-up (Table 1). Bivariate correlation analyses detected no collinearity problems for the covariates.

Table 1. Baseline characteristics of the original sample of COPD outpatients (n=220) and the subsample (n=99) included in both Cox models

Variables	n=220	n=99
Gender: male/ female (%)	114 (51.8)/ 106 (48.2)	54 (54.5) / 45 (45.5)
SST/ LMIS	109/ 111	50 / 49
Self-efficacy, range – 2–2	.11 (.88)	.06 (.84)
Social support, range 0–3	1.42 (.88)	1.51 (.87)
Descriptive norm, range 0–4	.97 (.84)	.91 (.76)
Attitude, range -1.5–1.5	.55 (.48)	.62 (.47)
Point prevalence quit rates SST/ LMIS (%)		
Baseline	1.8/ 1.8	4/ 2
Six months follow-up	23.9/ 18	38/ 30.6
12 months follow-up	21.1/ 11.7	34/ 18.4

Note. SST = SmokeStopTherapy, LMIS = Minimal Intervention Strategy for Lung patients. Characteristics are presented as means (standard deviation) or number (%).

Cox regression with time-varying covariates

Figure 1 shows the time-varying nature of the cognitive parameters (attitude, social support, descriptive norms and self-efficacy) for smokers and abstainers separately. Covariates values were standardized to facilitate interpretation. Figure 1 represents the standardized scores for all four cognitive covariates at baseline, six and 12 months follow-up.

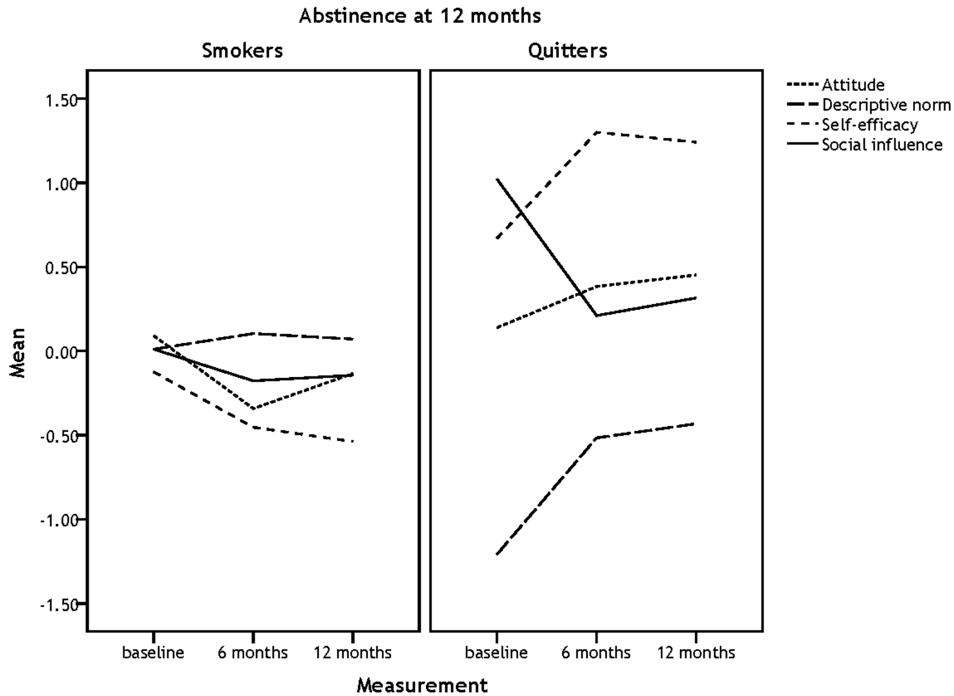

Figure 1. Cognitive development for smokers and abstainers separately over time (standardized scores), n=99

To capture both time periods in one model, Cox regression with time-varying covariates was fit to the data (n=99). This model indicated self-efficacy (p<.00) and descriptive norm (p<.01) to be significant covariates of smoking cessation, contributing uniquely to the final model. However, tests for violations of the PH assumption found evidence of non-proportionality, meaning that the hazard ratios for both time periods cannot assumed to be equal. Therefore, the interaction with time was tested in the model, resulting in self-efficacy as major predictor of smoking cessation, which hazard ratio increases considerably over time. Table 2 shows the remaining model, with an explained variance of 20.5% (Wald p<.00). Importantly, the coefficient of attitude approached zero, and showed no significant effect.

Table 2. Summary of time-varying Cox model for smoking abstinence, n=99 (198 cases)

	B	SE (*B*)	Robust SE (*B*)	Hazard Ratio	*95% CI*	*Z*	*p*
Step 1[a]							
Self-efficacy	.68	.14	.17	1.97	1.42 – 2.72	4.10	.00***
Descriptive norm	-.34	.14	.13	.71	.55 - .92	-2.58	.00**
Step 2[b]							
Time * Self-efficacy	2.11	.51	.33	8.26	4.29 – 15.88	6.33	.00***

Note. Indication for smoking status: 0 = smoking, 1 = smoking abstinence. **p<.001 ***p<.00. [a]R^2=.15, Wald test=20.7 (df=2), p<.00. [b]R^2=.205, Wald test=40.06 (df=1), p<.00.

Not all available information on covariates values was yet included in the analyses. Results of the model using mean values of the covariates to examine its contribution to smoking cessation at six and 12 months follow-up, confirmed the influential role of self-efficacy over time. The explained variance increased to 37.2% (Wald p<.00). The hazard ratio indicated that for each single scale point increase in level of self-efficacy (e.g. going from probably to definitely being confident to maintain non-smoking in tempting situations) the likelihood of reaching abstinence becomes 3.99 (*95% CI:* 2.90–5.51) times higher. Tests for violations of the PH assumption found no evidence of non-proportionality. Again, the coefficient of attitude approached zero, and showed no significant effect.

Cox regression analyses for fixed time periods

To explore the underlying mechanisms of the findings from the time-varying models, three Cox models for the separate time periods were fit to the data (n=99). Table 3 shows the results for these models following backward elimination procedures. Both attitude and descriptive norm were found as significant baseline covariates of point prevalence smoking cessation at six and 12 months follow-up. Respondents that scored high on descriptive norm were at higher risk of smoking, and thus had a lower chance to reach abstinence. For each scale point increase for attitude, the likelihood to stop smoking increased by respectively 2.32 and 2.84 at six and 12 months of follow-up. The significant contribution of attitude was in line with results from a previous study on the whole sample data [23]. The Wald test showed that both models contribute to explaining the likelihood of smoking cessation (p<.000), however the variances in smoking cessation explained by these covariates were low (respectively R^2=.089 and .068). When analyzing six months covariates for the prediction of smoking cessation at 12 months follow-up, a shift in results was observed. Now self-efficacy, and not attitude or descriptive norm, was found significant for smoking cessation. For each point increase on the scale of self-efficacy, the risk of smoking cessation increases by 4.35. Also, the explained variance increased considerably to 34.7%.

Table 3. Summary of the single-point Cox models for smoking abstinence, n=99 (198 cases)

Baseline covariates to predict smoking abstinence at 12 months follow-up[a]							
	B	SE (*B*)	Robust SE (*B*)	Hazard Ratio	*95% CI*	*Z*	*p*
Attitude	.84	.31	.30	2.32	1.35 – 4.62	2.81	.00**
Descriptive norm	-.58	.20	.19	.56	.38 - .81	-3.04	.00**
Baseline covariates to predict smoking abstinence at six months follow-up[b]							
Attitude	1.05	.27	.26	2.84	1.72 – 4.69	4.09	.00***
Descriptive norm	-.41	.17	.17	.66	.48 - .92	-2.49	.05*
Six months covariates to predict smoking abstinence at 12 months follow-up[c]							
Self-efficacy	1.47	.26	.17	4.35	3.12 – 6.07	8.63	.00***

Note. Indication for smoking status: 0 = smoking, 1 = smoking abstinence. *p<.05, **p<.01, ***p<.001. [a]R^2=.068. Wald test=14.06 (df=2), p<.00. [b]R^2=.089. Wald test=18.70 (df=2), p<.00. [c]R^2=.347. Wald test=74.49 (df=1), p<.001.

Discussion

This study is, to our knowledge, the first to investigate time-varying versus baseline analyses of smoking cessation determinants using commonly applied, predefined follow-up periods by means of Cox models. Three key findings resulted from comparing both approaches within the same dataset containing four current social cognitive determinants of smoking cessation. First, in contrast with the baseline analysis where self-efficacy appeared not to be predictive of abstinence at 12 months, from the time-varying analyses self-efficacy emerged as the strongest, unique, covariate of abstinence. Second, evidence was found for a bidirectional association between self-efficacy and smoking cessation in the present sample. Third, time-varying Cox regression analysis seems to be a valid and feasible way to examine the longitudinal mechanisms of smoking cessation, even when data from only three waves are available. Applying this analytical technique may add to our understanding of how cognitions interact with, and contribute to, the behavioral change process over time.

As we know, abstinence self-efficacy is generally considered to be an important mechanism through which abstinence is achieved and maintained [25,35] and several researchers have discussed the fluctuating role of self-efficacy in the process of smoking cessation [e.g. 12,14,21,36]. The present study showed that while using identical variables, the time-varying model produced considerably higher explained variance (20.5%) than the fixed baseline models (7 and 9%). The higher explanatory power of the time-varying analytical approach can be explained by two issues. First, the fact that the assessments included in the time-varying model were more proximal to the smoking status at six and 12 months follow-up than those included in the fixed baseline model is likely to have contributed to the greater predictive value of the time-varying model [12]. Second, as all subjects in this sample participated in a smoking cessation intervention and consequently the majority undertook at least one quit attempt during the first three months after baseline, both self-efficacy follow-up measurements were administered after a possible quit attempt. Cognitive and behavioral changes have been argued to be reciprocal. Changes in cognitions are predictive of behavior, i.e. having confidence in the ability to quit smoking has been shown to be an important predictor of smoking cessation [e.g. 15,17]. However, assessments of self-efficacy that are administered after a quit attempt may also reflect the consequence of the cessation outcome, as the smoker experiences how difficult it is to maintain abstinence in the presence of for example craving and withdrawal [3]. In our analyses a post-quit effect of behavior on self-efficacy may be derived from the time-varying analysis where mean values of covariates were applied, thus including the value of the 12 months covariate. This model showed an notably higher explained variance (R^2= 37%), which may be due to the 12 month self-efficacy value being dependent on prior quitting behavior. Additionally, the increasing observed explained variance of the second fixed time model using baseline covariates to predict six month cessation (R^2= 8.9%) and the last model with six months covariates to predict 12 month cessation (R^2= 34.9%) confirms this assumption (Table 3). As the six months measurement of the covariates was completed after a possible quit attempt, the data could partly reflect a cognitive reaction to a prior quit attempt and therefore could have contributed to the increased explained variance. Moreover, the effect of past behavior in predicting future behavior has been shown in many studies. Within the context of physical activity, for example, Hagger et al. [37] found that past behavior contributed an extra 19% variance to the prediction of physical activity over and above TPB variables. In extreme cases, past behavior was found to be the only unique significant predictor of prospective behavior [e.g. 38]. Summarizing, although the current study did not directly control for past behavior, a reciprocal relation between self-efficacy and smoking abstinence can be assumed.

The difference in outcomes of both analytic approaches in this study, and the role of attitude and self-efficacy in particular, has some theoretical implications. Although attitude at baseline appears to predict which smokers are more likely to benefit from participating in a cessation intervention, likelihood of abstinence seems to be insensitive to subsequent changes in attitude over time. Apparently, whether the intervention is successful in maintaining a positive attitude towards quitting is not decisive for the final outcome. Self-efficacy on the other hand, only becomes important during the behavior change process: participants that succeed in increasing or maintaining a high level of self-efficacy are more likely to (stay) quit. This also suggests that among this sample self-efficacy is more sensitive to changes in smoking status than attitude, and changes in self-efficacy during an intervention study may consequently be important indicators of treatment effects. From a practitioner's point of view, this implies that attitude might be a relevant factor when advising smokers on the cessation strategy most suited to their needs. And counselors should regularly monitor the level of self-efficacy during and after an intervention, and intervene in case of a decrease.

Input for the presented method consisted of the baseline and follow-up measurements at six and 12 months, which are common in trials in this field. Therefore, the applicability and feasibility of this analytical technique is high compared to other longitudinal techniques using multiple or even daily measures, such as ecological momentary assessment [2,12]. Although it seems to be a limitation to use (just) two time periods (0-6 months; 6-12 months) for describing time-varying changes in behavior, results from this study showed that the model's explained variance can be increased considerably, and that different covariates appear as significant indicators of behavior change. As our analytic approach does not put particularly high demands on the data required, we expect that many currently available datasets are suitable to replicate our analyses. Furthermore, the current approach may be of particular value in cases of missing endpoints. Although a 12 month follow-up is considered standard in this field, many published studies report shorter follow-ups. Our results suggest that with all available data the true abstinence within our sample could be estimated with 37% accuracy. This opens the possibility to model smoking abstinence at a future end points based on available cognitive parameters.

The following limitations should be taken into account. First, high drop-out rates for complete measures at several time points may limit the generalizability of the results, but unfortunately are common in trials in this field. In this case, the relatively high quit rates among the subsample included for this analysis, possibly reflects a selective drop-out of relapsed participants. However, the prospective prediction study of Christenhusz et al. [23] for the complete sample showed results similar to our baseline Cox model. Additionally, the current study compared two different analytic approaches within a single dataset. The drop-out issue does not affects this comparison as both statistical models used identical cases. Second, the current study was limited by the varying intervals between our measures and the moment smoking abstinence occurred. Respondents may have quitted only days after a measurement, in which case the cognitions were measured proximal to the behavior change, while others may have reached abstinence almost six months later.

Nevertheless, the results of this study suggest that time-varying Cox analyses is a valid and feasible approach to capture indicators of the behavior change process, even when using just two time periods. The complementarity of baseline versus time-varying analyses has been underlined in this study and suggests a bidirectional causal interaction between self-efficacy and smoking abstinence, in line with literature. As the presented method applied commonly used follow-up period and captured the important underlying covariates of abstinence, applicability for future studies can be suggested.

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6

A comparison of time-varying covariates in two smoking cessation interventions for cardiac patients

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Abstract

Background. To explore the time-varying contribution of social cognitive determinants of smoking cessation following an intervention on cessation. *Methods*. Secondary analyses were performed on data from two comparable RCTs on brief smoking cessation interventions for cardiac in- and outpatients. Cox regression with time-varying covariates was applied to examine the predictive cognitions for smoking cessation over time. *Results*. Both samples showed self-efficacy and intention to quit to be strong time-varying indicators of smoking cessation during the full one year follow-up period, and during the post-treatment phase in particular. Less consistently, time-varying cons of quitting and social influence were also found to be associated with smoking cessation, depending on the sample and type of intervention. *Conclusion*. Self-efficacy and intention-to-quit were the major covariates and positively related to smoking cessation over time among cardiac patients, in line with social-cognitive theories. Interestingly, both cognitive constructs appeared to act with some delay. Apparently, smoking cessation is a lengthy process in which the interplay between self-efficacy (and intention indirectly) and quitting behavior will largely determine long-term maintenance of abstinence. The presented time-varying analyses seem a valid and feasible way to underpin trajectories of cognitions in datasets with a limited number of time intervals.

Introduction

Social cognitive models in social psychology postulate that behavior is influenced by proximal cognitions regarding the specific behavior and by distal factors that may influence these cognitions [e.g. 1-3]. Multiple studies have been performed to examine the predictive value of cognitions in health-related behaviors [e.g. 4-9]. However, literature indicated there are some issues that should be addressed for analyzing predictor of health behavior. First, the before mentioned reviews and meta-analyses mostly rely on studies using variables measured at a single point in time to predict behavior change at some future endpoint and evidence exist for a fluctuating role of cognitions over time. Second, short-term predictions appear to be more accurate when compared to long-term predictions and lastly, an influential role of past behavior in addition to cognitive factors of behavior has been argued.

Research has shown cognitions to vary over time. For example, multiple studies have been performed on the dynamic role of self-efficacy over time [e.g. 10-14]. Thus, when applying a time-naïve method, such as a regression analysis, it is likely that critical information is lost.

Also, the length of follow-up between measurements of cognitions and subsequent measurement of behavior is held to be a limiting condition for prediction of health behavior [7,15]. For example, Theory of Planned Behavior (TPB) variables are most likely to predict behavior to the extent that they remain stable between the point at which they are measured and the point at which the behavior occurs and this should be less likely as the time interval increases [1]. The influence of cognitions on behavior may be quite temporary and not adequately captured by long time intervals. A recent meta-analyses on the prospective prediction of health related behaviors with the TPB found the strength of the intention-behavior relation to be highly variable, depending on the length of follow-up. Explained variances found in studies on detection behavior varied from 9% over longer-term follow-ups to 31.4% in shorter-term follow-up [7].

Besides long-term time intervals, accounting for the effects of past behavior has proved a challenge for the TPB [e.g. 16,17]. Within the context of physical activity, for example, a meta-analysis found that past behavior contributed 19% variance to the prediction of physical activity over and above TPB variables [16]. In extreme cases, past behavior has been found to be the only significant predictor of prospective behavior [e.g. 18]. Thus, there is no doubt that including a measure of past behavior improves the prediction of future behavior [8].

To capture time-varying covariates of behavior change, a time-varying analytical approach may be more suited since it includes all available information obtained in a study, including smoking status at several time assessments. Currently, available studies using time-varying analyses (e.g. ecological momentary assessment) controlling for smoking status are based on daily measures of covariates (such as cognitions) and outcome measures (such as smoking cessation, lapses and relapses) [e.g. 11,14]. Such studies are time consuming and usually not feasible. RCTs in the field of health promotion generally use no more than three follow-ups and commonly use intervals of multiple weeks to months. To explore such datasets for time-varying predictors of behavior, other analytical techniques are required. For these purposes, Cox regression analyses with time-varying covariates has several advantages. First, it does not require a normally distributed dependent variable and can therefore be applied to binary data (such as smoking cessation). Second, it is a multivariate technique and the covariates can be either continuous or categorical. Third, it can deal with censored data, that is, a case is censored if an event of interest is not recorded. Thus, it can account for the probability that a person may never reach smoking abstinence. Fourth, the analysis can be modified to handle recurring events. This means that a person can quit and relapse several times before reaching smoking abstinence. And finally, time-varying covariates can be included [19].

The present study performs a secondary analysis of data on comparable, behavioral (combined with pharmaceutical) interventions aimed at smoking cessation among cardiac outpatients [20] and inpatients [21]. A previously published multilevel analysis of the data from the first trial on cardiac outpatients examined the development of the cognitions attitude (both pros and cons), social support, intention to quit and self-efficacy over time as a result of the intervention [22]. The results showed that cognitions did change over time. Primarily in the early phase of the interventions a positive cognitive change was observed. Subsequently, the scores decreased significantly at all following waves. Wiggers et al. did not yet explore how these changes relate to the prediction of smoking status in a multivariate model.

Therefore, the aim of the current study is to analyze these cognitive predictors in time-varying analyses of two comparable intervention, using smoking status at multiple measurements as the dependent variable. Multiple cognitions of the ASE Model [3], now known as the I-Change Model [23], were examined over time, as well as the contribution of past behavior at baseline, several other known predictors of abstinence such as baseline nicotine dependency, and demographics.

Methods

For this study data were used from two RCTs, that are comparable with respect to population (cardiac patients), intervention (brief counseling with the minimal intervention strategy for cardiac patients (C-MIS)), follow-up length (12 months), and theoretical model (ASE Model). This enabled a comparison of the time-varying analyses across two independent samples. Past behavior at baseline was measured by asking if the patient had ever experienced at least one quit attempt. The dependent variable in both studies was point prevalence abstinence (PPA), which was assessed by patients' self-report measures of not been smoking during the past seven days [20,21].

Study 1: Smoking cessation among cardiac outpatients [20]

Participants and procedure. The sample consisted of 376 cardiac outpatients, randomized to the control group (n=188) or intervention group (n=188). All patients were offered free NRT for eight weeks, accompanied with application instructions from the nurse practitioner. Control patients received usual care only, i.e. no additional motivational counseling or self-help materials. In the experimental group patients were offered the behavioral intervention (C-MIS), consisting of 15-30 minutes of individual counseling by a nurse practitioner, self-help material and a follow-up telephone call by a nurse practitioner.

Measurements. Questionnaires were taken at five time assessments: baseline, and one week, two months, six months and 12 months after the intervention. Cognitive constructs were perceived positive (pros; T0; Cronbach's α=.81) and perceived negative consequences of quitting (cons; T0; Cronbach's α=.77), perceived social support (T0; Cronbach's α=.61), descriptive norm (T0; Cronbach's α=.45), intention to quit and abstinence self-efficacy expectations (T0; Cronbach's α=.94), according to the ASE Model [3]. Intention to quit was assessed by the stages-of-change algorithm (Transtheoretical Model [24]). According to this measure, only patients who smoke can vary in intention score, whereas quitters were automatically assigned the highest possible score. Therefore, we only included intention to quit as baseline (not time-varying) factor in the analyses. The social support construct consisted of two components: social stimulus and descriptive norm. Only social stimulus to quit smoking from important others in the environment was assessed at all five time assessments and included for analyses.

Study 2: Smoking cessation among cardiac inpatients [21, 25]

Participants and procedure. The sample consisted of 789 cardiac inpatients from 11 Dutch hospitals of which 401 patients were assigned to the control group and 388 to the experimental group. Control patients received usual care, indicating that no systematic attention was given to smoking. The experimental group received the C-MIS, which consisted of stop-smoking advice by the cardiologist, followed by 15–30 minutes of standardized bedside individual counseling and the provision of self-help materials by the ward nurse, and aftercare by the cardiologist at the hospital control visit after hospital discharge.

Measurements. Questionnaires were taken at three time assessments: baseline, and three and 12 months after the start of the intervention. Cognitive variables were intention to quit, perceived positive (pros; T0; Cronbach's α=.85) and perceived negative consequences of quitting (cons; T0; Cronbach's α=.57), social support (T0; Cronbach's α=.84), descriptive norms (T0; Cronbach's α=.50), and self-efficacy expectations (T0; Cronbach's α=.93). Most cognitive factors were measured according to the ASE Model [3,5].

Analyses

All subjects were included for analyses. Cox proportional hazard regression analysis with time-varying covariates was used to test the longitudinal relationship between potential predictors and smoking abstinence over the study period of one year using its predefined measurements at all follow-ups. This produces a dynamic survival model that reports hazard ratios, which are based on the combined follow-up data. A time-varying covariate is defined as any variable whose value for a given subject may differ over time [26].

For the Cox regression analyses survival libraries implemented in R packages were used (R foundation for statistical computing, 2009). Because data consist of multiple observations per subject, the robust variance estimate was used to account for the repeated observations of each subject [27]. All variables were included in the models as main effects. Potential for collinearity problems between the observed covariates was assessed with bivariate correlation analyses using PASW Statistics 18. In case of collinearity, only the strongest covariate was included in the analysis.

A Cox model with time-varying covariates was estimated using PPA measures at all follow-up assessments. Using this method, multiple different time periods were analyzed separately adjusted for the fact that the time periods within one patient are dependent [27]. Data were organized so that quit smoking at follow-up was predicted from the *mean* values of the social cognitive predictors of the preceding and current follow-up. Time intervals were characterized by the start and endpoint from the measurement period. The outcome of interest is PPA, a dichotomous variable classifying subjects as abstainers or smokers.

The Cox regression model was built in several steps. First, univariate analyses of the separate social cognitive variables in relation to PPA were conducted to provide insight in its contribution to smoking abstinence and into the shape of each variable's survival function (proportional hazard (PH) assumption). In the second step interactions with time were tested for those factors for which the PH assumption indicated that hazard ratios could not assumed to be equal for the different time periods analyzed. Significant interaction variables were left in the model ($p<.05$). For interpretation of the residual main effect, the interaction with time should be considered. All significant univariate factors were fit to the multivariate model, except for intention to quit which was fit last to the model. A backward elimination procedure was used to delete covariates from the Cox regression models which did not appear to contribute to the prediction of the outcome. These variables were eliminated individually until parameter estimates for all remaining variables were associated with p-values of less than .05.

Results

Study 1: Smoking cessation among cardiac outpatients

Table 1 shows the baseline characteristics for the control and the experimental group in this RCT. No significant differences were found. PPA rates at 12 months were 12% for the control group and 17% for the experimental group, which was non-significant. More details on the sample were reported elsewhere [20].

Table 1. Baseline characteristics of cardiac outpatients (study 1) for the C-MIS + NRT and NRT study arms

	Experimental	Control	*p*-value
n=372	n=186	n=186	
Age (mean, sd)	59 (12)	58 (12)	NS
Male (n, %)	118 (63)	115 (62)	NS
Education (n, %)[#]			
Low	107 (57)	125 (67)	NS
Middle	57 (31)	42 (23)	NS
High	22 (12)	19 (10)	NS
Nicotine dependency (n, %)	79 (43)	73 (39)	NS
Point prevalence abstinence (n, %)	1 (.05)	3 (1.6)	NS
Intention to quit (TTM) (1 = high intention, 6 = no intention to quit or reduce)	3.66 (.63)	3.68 (.65)	NS
Pros of quitting (0 = no pros, 3 = pros)	1.50 (.62)	1.58 (.60)	NS
Pros of smoking (cons) (0 = no pros, -3 = many pros)	-1.23 (.62)	-1.21 (.59)	NS
Self-efficacy (-2 = very difficult, 2 = very easy)	-.05 (1.02)	1.28 (.79)	NS
Social support (0 = no support, 3 = much support)	1.20 (.76)	-.05 (.96)	NS
Perceived behavior support (0 = everyone, 4 = nobody)	2.48 (.86)	2.49 (.85)	NS
Previous quit attempt (n, %)	157 (84)	151 (81.6)	NS

Note. [#]Low = vocational training; middle = advanced vocational training; high = high vocational/ university training. n=372 instead of 376 because four patients did not respond to the baseline questionnaire. Nicotine dependency = Fagerström score >6, sd = standard deviation, NS = not significant.

Time-varying analysis of smoking cessation

Figure 1 shows the time-varying nature of four cognitive factors (pros and cons of quitting, social support, and self-efficacy) for smokers and abstainers separately. It represents the standardized *z*-scores for all four cognitive factors at baseline, and one week, two, six and 12 months after the intervention. No collinearity problems were detected for these data.

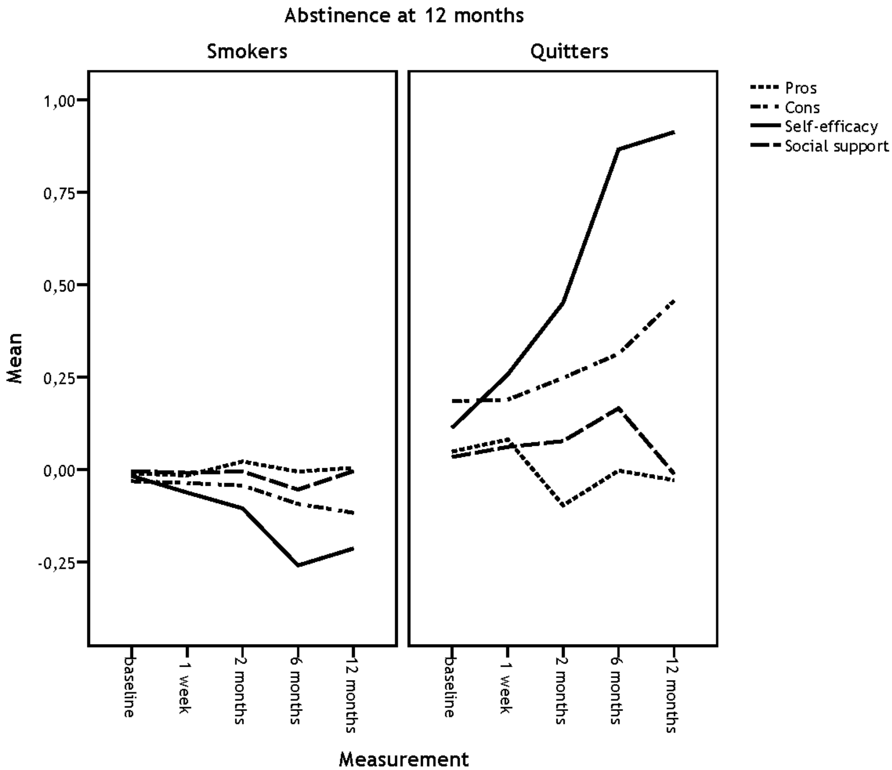

Figure 1. Cognitive development over time for smokers and quitters separately for cardiac outpatients (study 1)

To capture all time periods in one model, Cox regression with time-varying covariates was fit to the data (*n*=376). First, all factors (mean values) were univariately tested using time-varying Cox regression models. Both self-efficacy (*HR*=2.62, *95% CI*: 2.16–3.20) and cons of quitting (*HR*=1.56, *95% CI*: 1.30–1.87) were main cognitive indicators of smoking cessation over time. Additionally, smoking cessation at baseline (*HR*=1.12, *95% CI*: 1.04-1.20), intention to quit (stages-of-change; high – low intention) at baseline (*HR*=1.33, *95%*

CI: 1.15–1.55), and educational level (*HR*=1.12, *95% CI*: 1.00–1.26) were found significant when tested univariately. These factors were fitted to a multivariate time-varying Cox regression model. However, tests of the PH assumption indicated that hazard ratios could not be assumed to be equal for the different time periods analyzed. The coefficient for the interaction is positive and highly statistically significant: The effect of self-efficacy increased with time. That is, initially, self-efficacy had a negative partial effect on smoking cessation (given by the self-efficacy coefficient, -.87), which became progressively stronger with time at the rate of .79 per wave. This means the self-efficacy effect became only positive after the follow-up at one week after the intervention.

Eventually, four factors remained for the final time-varying model to be indicative for smoking cessation over time: The (residual) effect of self-efficacy, its interaction with time, PPA at baseline and the intention to quit at baseline (Table 2). Overall, the explained variance was 16.3%. All factors added significantly to this final model (Wald test=116.1, *df*=4, *p*=0).

Table 2. Summary of the time-varying final model of smoking cessation for cardiac outpatients (study 1) based on five measurements, n=376 (1504 cases, 18,9% missing)

	B	SE (*B*)	Robust SE (*B*)	Hazard Ratio	*95% CI*	*Z*	*p*
Self-efficacy	-.88	.24	.24	.42	.26 - .67	-3.61	.00***
Baseline intention to quit (TTM)	.21	.08	.08	1.23	1.05 – 1.44	2.58	.01**
Baseline point prevalence abstinence	.08	.04	.03	1.08	1.02 – 1.13	2.76	.01**
Time * Self-efficacy	.79	.10	.11	2.21	1.86 – 2.91	7.00	.00***

Note. Covariates were standardized. Indication for smoking status: 0 = smoking, 1 = smoking abstinence. ***p*<.01, ****p*<.001. Concordance =.73 (*se*=.02), R^2=.163. Wald test=116.1 (*df*=4), *p*=0.

Study 2: Smoking cessation among cardiac inpatients

Table 3 shows the baseline characteristics for the hospitalized smokers. Due to the randomization procedure, some differences were found in baseline characteristics between groups (see Table 3). These differences did not affect the current analyses as these do not directly test for intervention effects. More details on the sample were reported elsewhere [21,25].

Table 3. Baseline characteristics of cardiac inpatients (study 2) for the C-MIS and usual care study arms

	Experimental	*Control*	*p-value*
n=789	n=388	n=401	
Age (mean, sd)	56.2 (10.6)	57.3 (10.9)	NS
Male (n, %)	304 (78.4)	309 (77.1)	NS
Education (n, %)#			<.05
Low	206 (53.6)	195 (48.9)	
Middle	126 (32.8)	119 (29.8)	
High	52 (13.5)	85 (21.3)	
Nicotine dependency (n, %)	101 (29.8)	116 (33.7)	NS
Point prevalence abstinence (n, %)	102 (26.3)	84 (20.9)	<.001
Intention to (stay) quit (1 = very weak, 10 = very strong)	7.94 (2.32)	6.54 (3.11)	<.001
Pros of quitting (0 = no pros, 3 = many pros)	1.79 (.55)	1.67 (.64)	<.01
Pros of smoking (0 = no pros, -3 = many pros)	-1.29 (.70)	-1.33 (.73)	NS
Self-efficacy (-3 = very difficult, 3 = very easy)	-1.56 (1.27)	-1.66 (1.33)	NS
Social support (-3 = much discouragement, 3 = much support)	1.39 (.92)	-1.05 (.96)	<.001
Perceived behavior support (-1 = everyone, 1 = nobody)	.10 (.39)	.06 (.39)	NS
Previous quit attempt (n, %)	115 (30)	147 (36.8)	<.05

Note. #Low = vocational training; middle = advanced vocational training; high = high vocational/ university training. Nicotine dependency= Fagerström score>6, sd = standard deviation, NS = not significant.

PPA rates at 12 months follow-up were 30.9% within the control group and 42.3% within the experimental group. Bolman et al. [25] found a significant intervention effect on PPA at 12 months according to the intention-to-treat procedure, as well as according to a complete-case analysis. Figure 2 shows the cognitive development over time for smokers and quitters at 12 months follow-up.

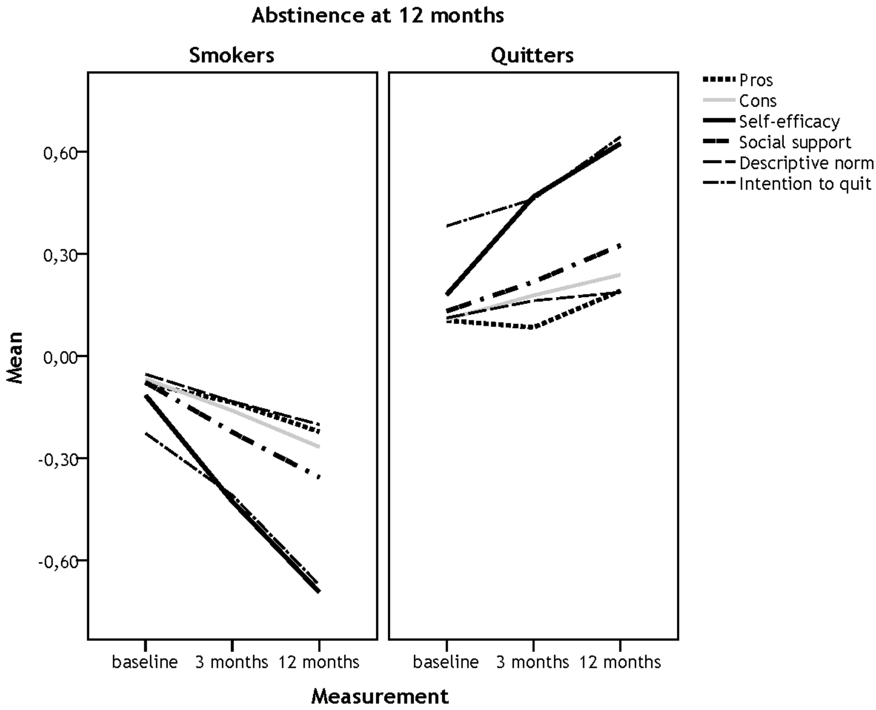

Figure 2. Cognitive development over time for smokers and quitters separately for cardiac inpatients (study 2)

Collinearity analyses indicate high correlation between the cons of quitting and self-efficacy. Univariate analyses showed that self-efficacy was stronger related to smoking cessation over time, compared to the cons of quitting. Therefore, the latter was excluded from all time-varying analyses.

First, univariate analyses of the time-varying cognitive factors were performed. Intention to quit (low – high intention) (*HR*=3.38; *95% CI*: 2.87–3.99) and self-efficacy (*HR*=2.09; *95% CI*: 1.90–2.30) were strongly related to smoking cessation over time. Also, pros of quitting (*HR*=1.50; *95% CI*: 1.32–1.70), social support (*HR*=2.07; *95% CI*: 1.84–2.32) and descriptive norms (*HR*= 2.00; *95% CI*: 1.74–2.31) were found significant in univariate time-varying analyses. Additionally, four baseline factors added significantly to smoking cessation when tested univariately: not having experienced a previous quit attempt before onset of the study (*HR*=.84; *95% CI*: .78-.92), being male (*HR*=.85; *95% CI*: .78-.93), being assigned to the intervention group (*HR*=1.24; *95% CI*: 1.15–1.34) and being quit at baseline (*HR*=1.10; *95% CI*: 1.02–1.19). The significant factors were fitted to a multivariate model, for which the PH assumption could not be assumed. For intention to quit an interaction with time was found (*HR*=4.05; *95% CI*: 1.96–8.37) and added to the model. This interaction effect indicates intention became more influential over time with a negative initial partial effect (*Β*=.78) for the intention to quit. The rate of 1.40 per wave indicates that the effect became progressively stronger with time with a positive effect at three months follow-up. Backwards elimination procedures resulted in the final model (R^2= 35.7%) presented in Table 4.

Table 4. Summary of the time-varying final model of smoking cessation for cardiac inpatients (study 2), based on three measurements, n=789 (1578 cases, 12.5% missing)

	Β	SE (*Β*)	Robust SE (*Β*)	Hazard Ratio	*95% CI*	*Z*	*p*
Intention to quit	-.78	.31	.39	.46	.21 – .99	-2.00	.05*
Self-efficacy	.50	.05	.05	1.65	1.49 – 1.83	9.75	.00***
Pros	-.17	.08	.07	.85	.73 - .98	-2.27	.02*
Descriptive norm	.32	.08	.07	1.38	1.20 – 1.59	4.51	.00***
Social support	.32	.07	.07	1.38	1.21 – 1.57	4.88	.00***
Gender	-.09	.04	.04	.92	.85 – .99	-2.11	.04*
Previous quit attempt	-.12	.04	.04	.88	.82 – .95	-3.16	.00**
Time*Intention to quit	1.40	.27	.37	4.05	1.96 – 8.37	3.77	.00***

Note. Indication for smoking status: 0 = smoking, 1 = smoking abstinence. Concordance =.86 (*se*=.02) *p<.05, **p<.01, ***p<.001. R^2=.357. Wald test=399.9 (*df*=8), *p*=0.

Discussion

Knowledge of the time-varying characteristics of motivational factors is important in order to understand the nature and importance of these motivational factors in understanding smoking behavior. This knowledge may contribute to improved treatment strategies for increasing smoking cessation. Therefore, time-varying motivational factors for smoking cessation were examined for two independent samples of smoking cardiac patients over a study period of 12 months. Changes in cognitions among cardiovascular patients following a behavioral smoking cessation intervention had already been shown in a previous study [22]. However, as in these analyses smoking cessation was not incorporated as dependent variable, no inferences about the relationship between the trajectory of cognitive predictors during the course of one year and abstinence at that time point can be made. Our time-varying analysis on these same data suggests that the initial positive change in cognitions was only observed for the whole group and did not hold for those who were quit at baseline. The interaction with time for intention (study 2) and self-efficacy (study 1) showed a progressively stronger effect with time, with an initial negative partial effect on smoking cessation. Around the end of the intervention periods, in both studies, the coefficient became positive. Thus, our analyses suggest an increasing trajectory of self-efficacy (and intention-to quit for study 2) for abstinent patients, but only after the initial treatment phase. This means that when patients are no longer supported by the intervention, both self-efficacy and intention to quit are particularly important constructs. This finding shows that cognitions may act upon intervention exposure by a delayed rate. However, it can be assumed that the observed increasing rate does partly reflect high self-efficacy of patients that had quit smoking at the first follow-up and remained quit over time. Nonetheless, this implies intervention should pay more attention to sustaining high levels of both self-efficacy and intention to quit over time.

Results showed that those with higher self-efficacy scores were more prone to (have) quit smoking successfully during the study period. In study 2, this interaction between time-varying self-efficacy and time was not found, which is probably due to the inclusion of time-varying intention (which was not fit to the model in study 1). Intention to quit has been shown to be an influential variable in multiple behavioral models and an important predictor for smoking cessation among cardiac patients [28] and is suggested to serve as a mediator for other cognitions, including self-efficacy [1,4]. Presumably, a time-varying effect of self-efficacy was incorporated in the effect of intention to quit, which is supported by the finding that self-efficacy univariately did explain a fairly large proportion of the variance in smoking status (18%), as by the finding that addition of intention to the multivariate model reduces the hazard ratio for self-efficacy. Furthermore, the strong role of self-efficacy in the behavior change process is in line with several theories of behavior change, as is confirmed in a recent meta-analysis examining the role of self-efficacy for smoking relapse [29].

Some caution should be taken to make simple causal inferences based on the current analyses, though. In the Cox regression models, mean values between two successive measurements of each factor were calculated to examine its association with smoking cessation at the last of these two measurements. This implies that the time-varying covariates are partly based on a value that coincides with the assessment of the dependent variable. Consequently, it can be presumed that the covariates partly reflect a cross-sectional or post-quit measure. As such, these factors cannot be regarded as merely predictors of behavior, but also incorporate an effect of behavior. Nonetheless, our findings clearly illustrate that the trajectory of self-efficacy co-varies with changes in smoking abstinence in the course of one-year follow-up. Multiple studies suggest the strong relation of post-quit measures of self-efficacy in contrast to a low explained variance due to pre-quit measures [e.g. 29]. In other words, evidence exists for a reciprocal relation of cognitions and behavior. Moreover, this suggests self-efficacy to be a more valid cognition for making inferences on the longer term, in contrast to for example attitude. The latter appears to act rather independently and less sensitive to changes in smoking status.

In both datasets two measures of social influence, social support and descriptive norm, were included. These covariates did not consistently contribute to the models, though. In study 2 among cardiac inpatients for both constructs a significant effect was found, which were not confirmed in study 1. This may be due to differences between the provided interventions. In study 1, both groups received NRT and one group additionally received the C-MIS counseling. Study 2 only delivered the C-MIS counseling to the experimental group. The provision of NRT may have interacted with these variables. Possibly less support from the environment is required to reach abstinence as withdrawal effects are mitigated by NRT usage. Another explanation might be that the cardiac inpatients (study 2) received more social support due to the higher severity of their disease, compared to cardiac outpatients (study 1) for which the need to quit is probably less urgent.

Although most outcomes of this study are consistent with literature, this did not apply to pros of quitting. In the analyses, two different subscales were used: pros and cons of quitting. The pros of quitting construct was either not associated or (slightly) negatively associated with smoking cessation over time in the multivariate analyses, in contrast to the assumption that a more positive attitude is predictive of smoking cessation [e.g. 30]. It could be that the pros of quitting may be a positively related baseline hazard for longer term behavior [31,32], but in a time-varying analysis appear to be less important and even negatively related to smoking cessation. In other words, a strong positive attitude helps people to engage in a behavioral change program committedly and as a result they may benefit more from the intervention than less motivated people. However, the positive attitude does not show to protect against relapse directly. Presumably, this is partly due to abstinence experiences during follow-up. Ajzen [30] already suggested a feedback effect on antecedent variables in the TPB, such as that behavior experiences lead to changed cognitions. Thus, as someone quits smoking, he or she could, for example, experience withdrawal effects and consequently adjusts the initial positive attitude towards quitting to a more negative one. Similarly, this feedback effect could explain the minimal role of previous quit attempts at baseline in the current analyses. Due to the time-varying inclusion of variables and smoking status, effects of past behavior were presumably reflected in these cognitions, mediating its hypothesized main effect suggested in previous studies [e.g. 16,30].

A few limitations are noted here. First, the outcome measure applied in the current analyses in both studies was the self-reported PPA, lacking biochemical validation at all measurements. Wiggers et al. [20] showed a deviating percentage quitters of approximately 7% in both intervention groups, comparing self-reported and biochemically validated abstinence at 12 months follow-up. Although a deception rate of 7% can be considered as low [33], this could explain some of the error variance in the presented models. A second limitation is that the reliability of the social influence and cons scales was not sufficient in study 2. Due to high collinearity with self-efficacy, the cons construct was removed from analyses. However, for the descriptive norm scale in study 2 and the social support scale in the study 1, the low scale reliability may have concealed effects of these constructs.

In summary, the present study showed that the trajectory of smoking behavior following smoking cessation interventions co-varies with changes over time in cognitive predictors. Changes in self-efficacy and the intention-to-quit, assessed three to five times during one year, were the major direct indicators of smoking cessation over time in two samples, largely in line with social cognitive theories. Remarkably, both cognitions had a small negative effect during the intervention phase, but this turned into a positive effect in the post-treatment phase and which grew stronger towards the end of the follow-up period. Our findings stress the importance of reevaluating trajectories of cognitive factors during the process of smoking cessation, to enable interventions to be more responsive to changes in cognitions. The presented time-varying analytical technique seems suitable for revealing mechanisms of behavioral change trajectories, as it can rely on data from commonly used designs with a limited number of follow-ups, and controls for intermediate changes in behavioral outcomes.

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7

Dealing with delayed behavioral effects in health promotion by modeling cognitive outcomes in cost-effectiveness analyses: a validation study

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Abstract

Background. Cost-effectiveness analyses (CEAs) of behavioral interventions typically use physical outcome criteria. However, any progress in cognitive antecedents of behavior change may be seen as a beneficial outcome of an intervention, assuming that this increases the likelihood to achieve successful behavior change in the (near) future. The aim of this study is to explore the feasibility and validity of incorporating cognitive parameters of behavior change in a CEA of behavioral interventions. *Methods*. The CEA of an existing dataset from a three-armed randomized controlled trial on smoking cessation was re-analyzed. First, relevant cognitive parameters that preceded behavior change in this dataset were identified. Second, six months cost-effectiveness results were calculated. Third, probabilities for the transition rate between combined states of smoking and cognitions at six weeks, and corresponding smoking status at six months were obtained from the dataset. Fourth, these rates were extrapolated to the time period from six to 12 months in a decision analytic model. Lastly, these simulated results were compared to the 12 months' observed cost-effectiveness results. *Results*. Self-efficacy was the strongest time-varying predictor of smoking cessation in the present sample (R = 25.6%) of 414 smokers. Six and 12 months observed CEA results for the multiple tailoring intervention (MT) versus usual care showed respectively €21,400 and €3,188 had to be paid for each additional quitter. Simulated 12 months CEA results indicated €10,600 had to be paid for each additional quitter. For the observed 12 months results, the probability of MT to be cost-effective was 88% at a willingness-to-pay of €18,000. For the simulated results the probability was 53%. *Conclusion*. The simulated CEA showed largely similar, but somewhat more conservative, results and was therefore validated by the true data. Using self-efficacy to enhance the estimation of the true behavioral outcome seems a feasible and valid way to estimate future cost-effectiveness outcomes.

Introduction

Cost-effectiveness analyses (CEAs) in health care research and public health are considered an important tool to help decision-makers to set funding priorities [1]. Exploring the cost-effectiveness of a behavioral health intervention, however, should have some implications for the CEA methodology used. Generally, health promotion interventions are designed to accomplish behavior change. CEAs of these interventions typically focus on objective outcome measures, i.e. physical endpoints such as weight loss, less alcohol consumption or biochemically validated smoking cessation [2,3]. However, behavior change is a complex process in which several steps need to be taken, including changes in cognitive antecedents of behavior change. Any progress in cognitive steps towards behavior change can be seen as a beneficial outcome of an intervention, assuming that this increases the likelihood to achieve successful behavior change eventually [4]. But to date such partial effects are ignored in randomized controlled trials (RCTs) as well as in CEA of such trials. As most intervention studies have a relatively short follow-up period of six months, it is likely that positive intervention effects are achieved after the follow-up period. Not accounting for this delayed behavior change may lead to biased estimates of (cost) effectiveness of behavioral interventions [2,5-10]. An alternative way to the demanding approach of extending relatively short follow-up periods and expanding the range of outcome measures is to use intermediate, cognitive determinants of behavior to model behavior change over a longer period.

Cognitive determinants of behavior can predict health behavior change [e.g. 11-16]. As a consequence, progression (or decline) in these determinants can be seen as partial behavior change. The cognitive determinants are derived from theories, which are used to explain and predict behavior (change) [e.g. 12,17]. Examples are the Transtheoretical model (TTM) [18], the Theory of Planned Behavior (TPB) [11,19], the Social Cognitive Theory (SCT) [14] and the I-Change Model [20]. These theories define cognitive antecedents of behavior change, and state that behavior is a result of determinants such as intention, self-efficacy and attitudes.

Few studies have been conducted on the inclusion of partial behavior change in CEAs by means of changed cognitions. Our recent review on the role of cognitions in CEAs of behavioral interventions found that the use of cognitive parameters in calculating cost-effectiveness outcomes is to some extent recognized, but still in its infancy [3]. One of the frameworks that was distinguished when considering the inclusion of cognitions in CEA, consisted of a approach to model final behavioral endpoints based on intermediate, cognitive measures of behavior change.

To our knowledge, only three studies have modeled partial behavior change in CEAs of behavioral interventions [2,9,10]. In all three studies stages-of-change data [18] were modeled to predict future behavior change. Wagner & Goldstein [2], for instance, presented a hypothetical example of incorporating these stages in CEA methodology and concluded that CE results may be biased by ignoring partial effects. A CEA of a computer-based cessation intervention in primary care by advancing a smoker's cognitive stage-of-change (TTM) also showed that effects may be underestimated by solely focusing on the physical outcome of smoking cessation [10]. Also, the results of our recent study showed that the already dominant intervention at one year follow-up became even more dominant after modeling the 12 months stages-of-change to a two years follow-up, which corroborates the underestimation of ignoring partial effects [9].

In the present study, partial behavior change was modeled in a CEA of two behavioral interventions for smoking cessation by means of cognitions derived from social cognitive theories. An important distinction between stage-based theories such as the TTM and (non-stage-based) social cognitive theories such as the TPB is that the former classifies subjects according to a discrete stages-of-change algorithm (readiness to change) while the latter consist of dimensional variables that are assumed to predict and explain behavior change. Much research is available describing the transition probabilities for the stages-of-change of the TTM [e.g. 21-28]. These are lacking for non-stage-based, dimensional theories, which do not distinguish qualitatively different states, but provide a multidimensional change continuum. Also, these cognitions appear to behave dynamically through the behavior change process, and variations over time have shown to be predictive of behavior change [e.g. 29-31]. Therefore, to use these cognitive determinants in a predictive cost-effectiveness model, a time-varying analysis should be employed to identify relevant cognitions of behavior change.

The aim of this study was to model cognitive parameters into a cost-effectiveness model of two behavioral interventions in order to explore the feasibility and validity of incorporating partial behavioral change in CEAs. For this purpose, we used an existing dataset of a RCT on two Internet-based smoking cessation interventions that were compared to usual care for their cost-effectiveness at 12 months follow-up. We replicated its CEA calculating cost-effectiveness results at six months follow-up and modeled partial behavior change estimates to predict cost-effectiveness results at 12 months. To accomplish this, several steps were taken. First, relevant cognitive parameters that precede smoking cessation were identified. Second, intermediate six months cost-effectiveness results were calculated. Third, probabilities for the transition of intermediate to final endpoints (i.e. behavior) were obtained from the data. Fourth, these rates were applied to estimate smoking cessation at 12 months in a decision analytic cost-effectiveness model. Lastly, these simulated CEA outcomes were compared with the observed trial-based CEA outcomes.

Methods

Sample

Data from the PAS (Personal Advice in Stopping smoking) study were used [32]. The PAS study is three-armed randomized controlled multi-center trial with one year follow-up that evaluated the (cost-)effectiveness of an Internet based multiple tailored smoking cessation program with (MTC) and without (MT) tailored counseling by practice nurses, compared to care as usual (CAU) consisting of standard practice. A total of 414 smokers were included in the PAS study and randomly assigned: 163 received MTC, 132 received MT and 119 received CAU. All missing patients at the follow-ups were assumed to be smokers. More details on the PAS study design are published elsewhere [32].

Baseline characteristics are presented in Table 1. No significant baseline differences were found regarding demographics, cognitions or costs between the three treatment arms, except for self-efficacy. Participants randomized to the CAU group appeared to have a significant lower self-efficacy towards quitting, compared to both intervention groups.

Table 1. Baseline characteristics of the three treatment arms of the PAS study (n=414)

	MTC	MT	CAU	*p*-value
n=414	n=163	n=132	n=119	
Age (mean, sd)	48.1 (12.0)	47.8 (12.5)	48.1 (11.3)	NS
Male (n, %)	60 (36.8)	55 (41.7)	51 (42.9)	NS
Education (n, %)#				
Low	56 (34.4)	38 (28.8)	39 (32.8)	NS
Middle	68 (41.7)	63 (47.7)	56 (47.1)	
High	39 (23.9)	31 (23.5)	24 (20.2)	
Intention to quit (mean, sd) (1 = very surely not, 7 = very surely yes)	6.41 (.71)	6.40 (.73)	6.24 (.78)	NS
Intention to stay quit (mean, sd) (1 = very surely not, 7 = very surely yes)	6.21 (.87)	6.20 (.87)	5.97 (.93)	NS
Pros of quitting (mean, sd) (1 = no pros, 5 = many pros)	3.62 (.80)	3.50 (.70)	3.47 (.76)	NS
Pros of smoking (mean, sd) (1 = no pros, 5 = many pros)	2.52 (.76)	2.54 (.76)	2.53 (.67)	NS
Self-efficacy (mean, sd) (1 = surely not, 5 = surely yes)	3.45 (.73)	3.45 (.68)	3.11 (.77)	<.001
Social support (mean, sd) (1 = no support, 5 = much support)	3.64 (.88)	3.53 (.92)	3.47 (1.02)	NS
Social modeling (mean, sd) (1 = nobody, 1 = all of them)	2.63(1.09)	2.86 (1.03)	2.82 (1.12)	NS
Social norms (mean, sd) (1 = no smoking norm, 5 = smoke norm)	1.73 (.99)	1.88 (1.11)	1.76 (.76)	NS

Note. #Low = vocational training; middle = advanced vocational training; high = high vocational/ university training, sd = standard deviation, NS = not significant.

The PAS study

The PAS study compared the more intensive MTC program, the less intensive MT program and CAU. In the MT program, respondents received a total of four feedback letters: at baseline, two days after the quit date, after six weeks and after six months. Feedback was personalized, adjusted to changes a respondent had made since inclusion and tailored to several respondent characteristics: gender, cognitive variables (attitude, social influence and self-efficacy), intention to quit smoking, goal and relapse prevention strategies (action and coping plans), and smoking behavior. In the MTC program, respondents received a counseling session by their practice nurse instead of the third tailored feedback letter at six weeks follow-up and an additional telephone contact after six months [32]. CAU consisted of standard practice and could vary from a brief intervention consisting of a single stop smoking advice to more intensive interventions consisting of at least four consultations [33].

Measurements

Baseline characteristics and cognitive determinants of behavior change were collected using a written questionnaire consisting of 54 questions based on the I-Change model [20]. Variables relevant to the present study included demographics (gender and education level), intention to quit (single combined item of intention to quit and stay quit), self-efficacy (eight items, Cronbach's α=.89), social norm (three items, Cronbach's α=.76), social support (three items, Cronbach's α=.61), social modeling (three items, Cronbach's α=.36), pros of quitting (six items, Cronbach's α=.72), cons of quitting (six items, Cronbach's α=.66) and having experienced a previous quit attempt at baseline (dichotomous single item). The Likert scales used are in principle considered to produce ordinal data. However, there appears consensus in methodological literature that these scales in general result in findings similar to data obtained with interval scales [35-37]. Measurements at baseline, six weeks, six months and 12 months were used for analyses.

Self-reported point prevalence abstinence was the primary outcome of the present study, assessed by one item asking whether the respondent had refrained from smoking during the past seven days (0 = yes, 1 = no). Although Smit et al. [34] focused on prolonged abstinence (i.e. being abstinent from smoking for at least six months) this was not possible in the present study due to the short-term variations in cognitions and behavior that were accounted for in this study.

Time-varying regression analyses

Time-varying regression analyses were used to select the relevant cognitions to be included in the prediction model. Cox proportional hazard models with time-varying covariates were fit to test the longitudinal relationship between potential social cognitive factors (intention to quit, pros and cons of quitting, self-efficacy, social norms, social support and social modeling) and smoking abstinence (point prevalent abstinence) over the study period of one year using its predefined measurements at baseline, six weeks, six and 12 months of follow-up. Also gender, education level, intervention and having experienced a previous quit attempt were additionally tested. This produces a time-varying survival model that reports covariate effects as a hazard ratio, also interpreted as relative risks. The hazard ratios are based on the combined follow-up data. It is presumed that the log hazard ratio is additively related to the covariates by the linear predictor [38]. This leads to the assumption of proportional hazards (PH assumption), which implies that the ratio of two hazards is independent of time [38,39]. To describe the dynamic development of the hazards, the Cox PH model can be modified to a dynamic Cox model by allowing the effects to vary with time [38]. A time-varying covariate is defined as any variable whose value for a given subject may differ over time. We used mean values between time assessments for the time-varying covariates to be able to incorporate values of all four measurements in the analyses. Mean cognitive values for the period from baseline to six weeks, six weeks to six months and from six to 12 months follow-up were calculated to examine its relation to smoking cessation at six weeks, six and 12 months follow-up.

The Cox model analyses different time *periods*, which were characterized by the start- and endpoint between two measurements. As participants could quit smoking and relapse in the same time period, subjects that reached the event of abstinence should not automatically leave the model as in regular survival analysis, but continue the process of quitting after cessation. Therefore, it is necessary that each time period for an individual appears as a separate observation. Additionally, we adjusted for the fact that the time periods within one patient are dependent [39]. Because data consist of multiple observations per subject, the robust variance estimate was used to account for the repeated observations of each subject [39,40]. A backward elimination procedure was applied to remove predictors from the Cox models which did not appear to contribute significantly to the outcome ($p<.05$). These variables were eliminated individually until parameter estimates for all remaining variables were associated with p-values of less than .05.

For the Cox models survival libraries implemented in R packages were used [39]. All cognitive variables were included in the models as main effects. The possibility of collinearity between the observed covariates was assessed with bivariate correlation analyses using SPSS 18.0.

Six months cost-effectiveness

Cost-effectiveness was calculated for the six months time horizon. This analysis was conducted from a societal perspective, corresponding to the original 12-months economic evaluation study [34]. Intervention costs, health care costs as well as patient costs were identified as relevant. These costs were assessed using a three month retrospective costing questionnaire consisting of open-ended questions and administered at six weeks, six months and 12 months follow-up. Health care and patient costs were valuated using the updated version of the Dutch manual for cost analysis in health care research [41]. All cost prices were indexed to the year 2011. A more detailed prescription of the measurement and valuation of costs were described by Smit et al. [34]. Incremental costs and effects were calculated for both treatments and CAU. Subsequently, NMBs (net monetary benefits) were calculated enabling us to compare the three groups directly with each other regarding their cost-effectiveness. Using a range of thresholds for the willingness to pay (WTP), the likelihood was calculated that each treatment would be most efficient. This was visualized by means of cost-effectiveness acceptability curves (CEACs). All analyses were conducted according to the intention-to-treat principle.

Uncertainty analyses. Sampling uncertainty around the estimates of cost-effectiveness and cost-utility was taken into account using non-parametric bootstrap re-sampling techniques (1,000 replications). Bootstrap analyses were conducted using Microsoft Office Excel 2007. All other analyses were conducted using SPSS 18.0.

Simulated 12 months cost-effectiveness

To predict smoking status at 12 months follow-up by means of information on smoking status and cognitive parameters(depending on Cox regression results), a predictive model was needed. Decision trees were used to outline the smoking and cognitive states a respondent could experience over the time frame of six to 12 months. These pathways were used to calculate future behavioral change, the associated costs and subsequently the incremental cost-effectiveness of the three study groups. Probabilities were extracted from the data to determine the distribution in categories consisting of a combination of smoking behavior and level of cognition per treatment arm at six months follow-up. Thus, participants were divided in separate ‘states’ of the cognition(s). For example, for self-efficacy questions were answered on a 5-point Likert scale. A person can therefore be in a category of being a smoker and having a low level of self-efficacy. Additionally, a separate state was included for those with missing values on self-efficacy.

For the predictive model, only the strongest predictor of behavior change was included for two main reasons. First, the dataset was restricted due to its sample size. Dividing multiple states would increase the need for more data, as otherwise several states or categories would be empty. Furthermore, increasing complexity results in a 'bushy' decision tree, which reduces its feasibility.

Transition probabilities. Rates for estimating the transition from six months' intermediate outcomes to 12 months' final behavior were based on rates from six weeks to six months follow-up observed in the data. In other words, to predict future behavioral change by means of smoking behavior and the value of cognition(s), probabilities were calculated between being in a certain category of a smoke-cognitive combination at six weeks of follow-up and smoking status at six months of follow-up. A precondition for applying this method is that tests for the proportional hazard assumption in the Cox regression analyses should be non-significant, meaning that the hazard ratios can be assumed to be similar across time periods. Transition probabilities were calculated for both treatment arms and CAU.

Costs. Costs were based on the costs of the PAS study for the first six months follow-up. For the six to 12 months follow-up, intervention costs were set to 0. Summed mean costs regarding general practitioners, medical specialists, hospital, alternative healer, mental health care, prescribed and 'over the counter' medication, medical aids and assistive devices and other care were included in the analyses. Because of the different expected costs associated with smoking status, we calculated separate costs for smokers and quitters, based on smoking status at six months follow-up. Effects were not discounted for time preference.

Cost-effectiveness analysis. Both costs and effects were estimated for the treatment arms and CAU by means of the predictive model for 12 months follow-up. Incremental costs and effects were thereafter calculated for each of the three treatments studied. After uncertainty analyses as described below, NMBs were calculated and the results were plotted in a CEAC.

Uncertainty analyses. All variables were evaluated for uncertainty in sensitivity analysis. Uncertainty regarding data inputs was quantified by means of Monte Carlo simulation with 1,000 iterations to explore the variation of the total costs as well as the costs per quitter, and the amount of quitters by varying all cost parameters and distribution (six months) and transition probabilities (six to 12 months) simultaneously over their ranges and the associated 95% confidence intervals. A gamma distribution was assumed for all costs and a logistic normal distribution for all probabilities. Sensitivity analyses were performed using @Risk5.5 for Excel (Palisade Corporation, 2010).

Results

Time-varying Cox regression analyses

All cognitive variables added significantly to the prediction of smoking cessation when tested univariately, except for the pros toward quitting. In addition, being highly educated and having experienced a previous quit attempt showed a significant positive effect on cessation. Figure 1 shows the cognitive development over time for all cognitions for both smokers and quitters at 12 months follow-up.

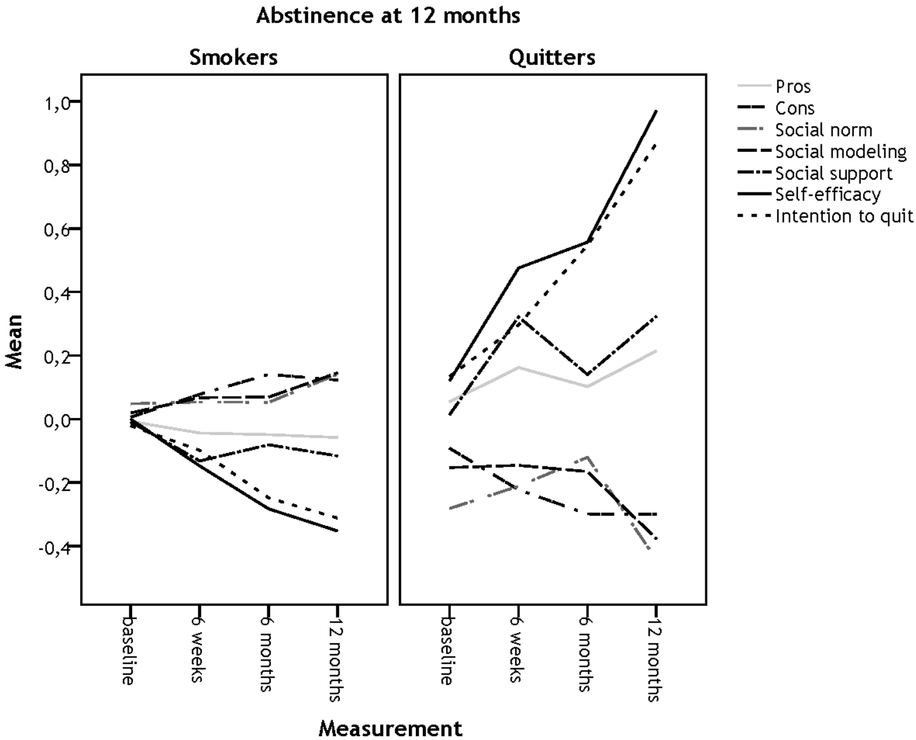

Figure 1. Cognitive development over time for smokers and quitters at 12 months

Univariate significant predictors were fit to the multivariate Cox regression model to examine their independent association with smoking cessation. Table 2 shows the final time-varying model.

Table 2. Summary of the final time-varying model of smoking cessation for the PAS study based on four measurements, n=414 (890 cases, 28.3% missing)

	Β	SE (*Β*)	Robust SE (*Β*)	Hazard Ratio	*95% CI*	*Z*	*p*
Self-efficacy	1.54	.14	.13	4.68	3.61–6.08	11.56	.00***
Intention to quit	.40	.13	.11	1.49	1.20–1.85	3.66	.00***
Social modeling	-.43	.11	.11	.65	.53-.80	-4.04	.00***
Baseline previous quit attempt	.11	.06	.05	1.12	1.01–1.24	2.21	.03*

Note. Covariates were standardized. Indication for smoking status: 0 = smoking, 1 = smoking abstinence. **p*<.05, ****p*<.001. Concordance =.86 (*se*=.03), R^2 =.282. Wald test=252.9 (*df*=4), *p*=0.

Self-efficacy added 25.6% to the explained variance in smoking cessation over time when tested univariately (*Β*=1.76, *HR*=5.83, *95% CI*: 4.60–7.38, *p*<.001). Intention to quit added 11.8% to the explained variance (*Β*=1.06, *HR*=2.90, *95% CI*: 2.34–3.58, *p*<.001. Tests for the proportional hazard assumption indicated that for the multivariate model, hazard ratios could be assumed to be equal for all time periods analyzed. For social modeling the univariate explained variance was 4.4% and having experienced a previous quit attempt at baseline showed an explained variance of .3% (*Β*=.10, *HR*=1.11, *95% CI*: 1.01–1.22, *p*<.05.

As self-efficacy showed by far to be the strongest predictor of smoking cessation over time, this covariate was selected for use in the prediction of future behavior change in the CEA of MT, MTC and CAU.

Prediction model

Six months distribution of participants. Of the respondents assigned to CAU, 84.9% (*95% CI*: 78.3-92) smoked at six months, in the MT group 83.3% (*95% CI*: 76.8-90.4) smoked and in the MTC group 84.7% (*95% CI*: 79.1-90.3) self-reported to have been smoking during the past seven days. Table 3 shows the distribution of respondents according to their six months' smoking status and level of self-efficacy.

Table 3. Probabilities for distribution of respondents among states of smoking status and self-efficacy at six months

Smoking status, self-efficacy	n	*p* (*95% CI*)	n	*p* (*95% CI*)	n	*p* (*95% CI*)
	CAU (n=119)		MT (n=132)		MTC (n=163)	
S, 1	4	.040 (.001-.122)	3	.027 (.001-.058)	1	.007 (.001-.021)
S, 2	6	.059 (.012-.157)	5	.045 (.005-.085)	8	.058 (.018-.098)
S, 3	13	.129 (.062-.269)	11	.11 (.05-.169)	19	.138 (.079-.197)
S, 4	4	.040 (.001-.079)	1	.009 (.001-.027)	16	.116 (.061-.171)
S, missing	74	.733 (.645-.821)	90	.818 (.744-.891)	94	.681 (.602-.760)
Q, 1	0	.000*	0	.000*	0	.000*
Q, 2	0	.000*	0	.000*	0	.000*
Q, 3	3	.167 (.001-.343)	0	.000*	1	.04 (.001-.118)
Q, 4	15	.833 (.657-.999)	21	.955 (.867-.999)	23	.92 (.811-.999)
Q, missing	0	.000*	1	.045 (.001-.133)	1	.04 (.001-.118)

Note. S = Smoker, Q = Quitter, missing = missing value, 1 (low) – 4 (high) = categories of self-efficacy. CAU = usual care, MT = Multiple Tailoring intervention, MTC = Multiple Tailoring plus Counseling intervention, n = number of participants, *95% CI* = 95% Confidence Interval, *p* = probability of being in a certain smoke-cognition category at six months. *The assumption was made that for the actual point values of 0, the point value was .001.

Transition probabilities. To predict future behavioral change by means of smoking behavior and self-efficacy, probabilities were calculated from being in a certain (0 = smoker or 1 = quitter) smoking status and a state of self-efficacy (1–4 and missing) at six weeks of follow-up to having a 0 or 1 smoking status at six months follow-up for each treatment arm. For self-efficacy, construct means were divided in the following categories: 1 = 1–1.99; 2 = 2-2.99; 3 = 3-3.99; and 4 = 4-5. Transition probabilities for each treatment arm are shown in Table 4.

Table 4. Transition probabilities for state at six weeks (smoking status, self-efficacy) to being a smoker at six months follow-up

Smoking status, self-efficacy	n	*p* (*95% CI*)	n	*p* (*95% CI*)	n	*p*(*95% CI*)
	CAU (n=119)		MT (n=132)		MTC (n=163)	
S, 1	3	.99**	0	.499† (.001-.999)	1	.499 (.001-.999)
S, 2	17	.944 (.836-.999)	12	.99**	14	.875 (.71-.999)
S, 3	9	.818 (.585-.999)	14	.875 (.71-.999)	23	.92 (.811-.999)
S, 4	3	.75 (.317-.999)	8	.800 (.547-.999)	15	.882 (.726-.999)
S, missing	56	.949 (.892-.999)	67	.971 (.931-.999)	71	.986 (.958-.999)
Q, 1	0	.499† (.001-.999)	0	.499† (.001-.999)	0	.499† (.001-.999)
Q, 2	0	.499† (.001-.999)	0	.499† (.001-.999)	0	.499† (.001-.999)
Q, 3	3	.99**	1	.499 (.001-.999)	1	.333 (.001-.877)
Q, 4	10	.476 (.258-.693)	7	.318 (.119-.517)	13	.464 (.276-.652)
Q, missing	0	.499† (.001-.999)	1	.99 (.927-.999)	1	.499† (.001-.999)

Note. For quitters transition probabilities are (1-*p*). S = Smoker, Q = Quitter, missing = missing values, 1-4 = categories of self-efficacy. CAU = usual care, MT = Multiple Tailoring intervention, MTC = Multiple Tailoring plus Counseling intervention, n = number of participants, *95% CI* = 95% Confidence Interval, *p* = transition probability between being in a certain smoke-cognition category at six months and smoking status at 12 months. *The assumption was made that for the actual point values of 0, the point value was .001. **The assumption was made that for the actual point values of 1, the point value was .99. †The assumption was made that for categories were no cases were present for smokers and quitters, the probability was .499.

Costs. Six months' costs for smokers (€611) and quitters (€439) were extrapolated to the time period of six to 12 months follow-up in the model. Mean costs per category, as well as mean total costs were among the input parameters for the simulation model.

Decision analytic model. Figure 2 shows a part of the decision analytic model for the distribution among those who had quit and their cognitive states (Q1 = quit, low self-efficacy to Q4 = quit, high self-efficacy) after six months of follow-up, the transition probabilities for the prediction of future behavioral change at 12 months follow-up and their associated costs for the MTC treatment arm of the PAS study.

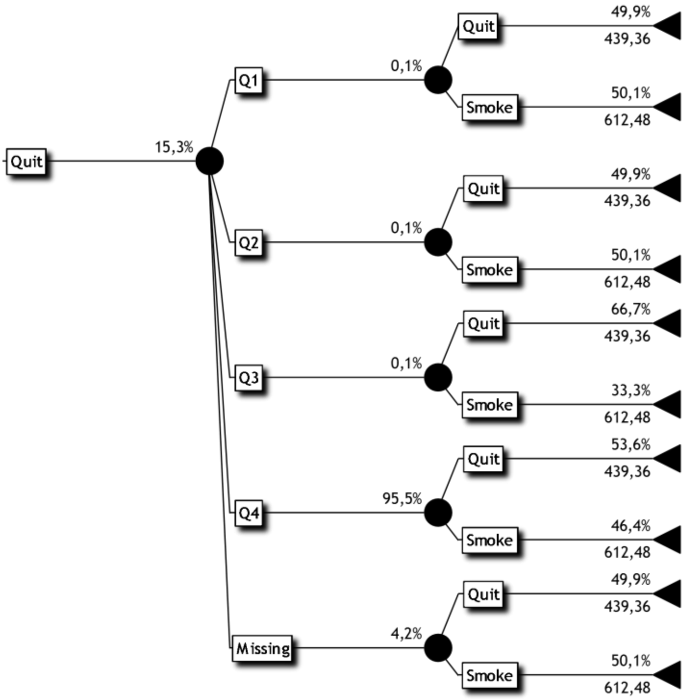

Figure 2. Decision analytic tree of pathways for the 'quitters' (Q) arm of the MTC treatment group for the time frame of six to 12 months, including percentages and costs (€)

Cost-effectiveness results

Observed CEA results at 12 months showed that for respondents in the MTC group costs were higher, while effects were lower than in the CAU and MT groups. Thus, MTC was dominated by the other two treatments. For the MT group, €5,100 has to be paid for each additional respondent being (prolonged) abstinent [34]. In the present study, however, we focused on point prevalence abstinence, for which analyses showed similar results. MTC was dominated by the other two treatments and for the MT group, €3,188 has to be paid for each additional respondent being abstinent.

For six months, the mean total costs for each participant within the MTC group during the first six months were €770, €538 for the MT and €324 for the CAU group. Self-reported quitting was respectively 17%, 18% and 17%. Cost per quitter were €4,530 within MTC, €2,990 within MT and €1,872 within the CAU group. The costs generated by subjects of the CAU group were thus considerably lower. Table 5 shows the MTC to be dominated by both MT and CAU and the incremental costs per quitter for MT versus CAU were estimated at €21,400.

Simulated results for the cost-effectiveness at 12 months (Table 5) showed higher costs and lower effects, compared to six month's cost-effectiveness. Cost per quitter were €12,355 within MTC, €7,507 within MT and €7,031 for participants receiving CAU. Again, MTC was dominated by CAU and the MT intervention. The incremental costs per quitter for MT versus CAU were €10,600. The simulated CEA showed that until a threshold value for the WTP of €10,600 per abstinent respondent, CAU was probably the most efficient treatment.

Table 5. Incremental costs (€) and effects per abstinent smokers for the three treatment groups studied

Intervention	Costs per participant	Probability abstinent	Incremental costs	Incremental probability abstinent	Incremental costs per quitter
Six months observed CEA results					
CAU	324	.17	-	-	-
MT – CAU	538	.18	214	.01	21.400
MTC – CAU	770	.17	446	0	Dominated
MTC - MT	770	.17	232	0	Dominated
Twelve months simulated CEA results					
CAU	914	.13	-	-	-
MT – CAU	1126	.15	212	.02	10.600
MTC – CAU	1359	.11	445	-.02	Dominated
MTC - MT	1359	.11	233	-.04	Dominated

Note. CAU = usual care, MT = multiple tailoring, MTC = multiple tailoring and counseling

Uncertainty analyses

Bootstrap analysis took into account the sampling uncertainty around the estimates of the trial-based six and 12 months cost-effectiveness results. For the 12 months simulated results probabilistic sensitivity analysis was employed to analyze the robustness of the above mentioned findings. The cost-effectiveness probabilities regarding a WTP of €18,000 for the observed six months and observed and simulated 12 months results are visually displayed in the CEACs (Figures 3 and 4).

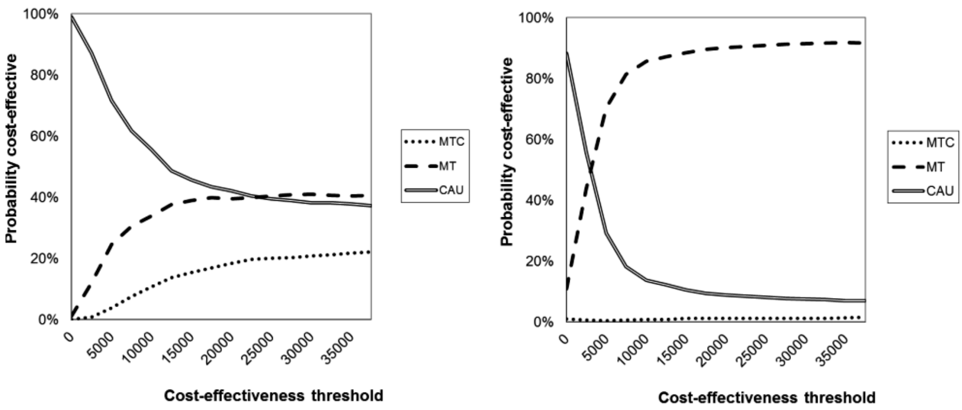

Figure 3. Six (left) and 12 months (right) observed cost-effectiveness acceptability curves

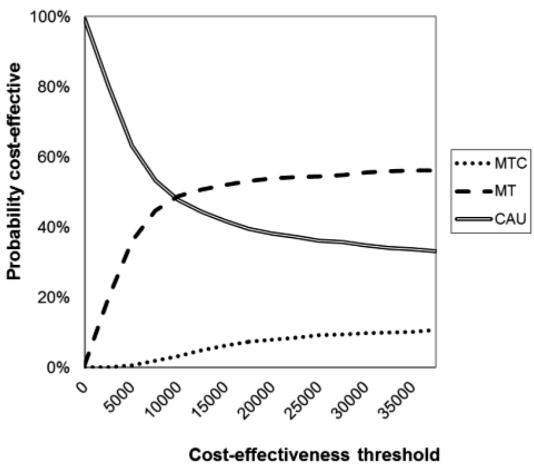

Figure 4. Simulated 12 months cost-effectiveness acceptability curve

The bootstrap results of the cost and effects for MT versus CAU for the both the observed and the simulated 12 months results are displayed in Figure 5. The cost-effectiveness plane of the simulated CEA shows that the uncertainty regarding the cost-effectiveness of MT versus CAU has increased considerably compared to the bootstrap results of the observed, trial-based CEA.

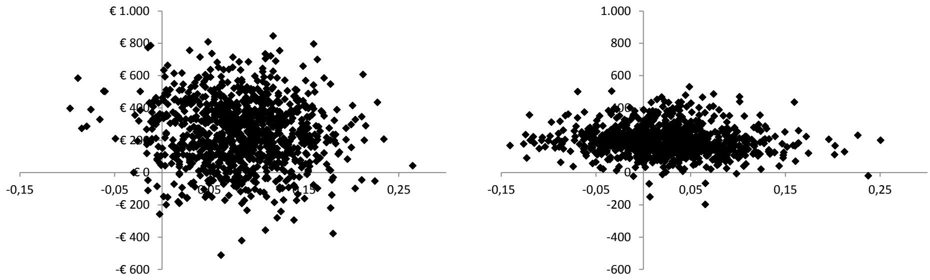

Figure 5. Cost-effectiveness planes for observed (left) and simulated (right) incremental costs and effects at 12 months for MT versus CAU

Discussion

The aim of this study was to model cognitive parameters into a cost-effectiveness model of a behavioral intervention in order to explore the feasibility and validity of incorporating partial behavioral change based on non-stage-based cognitions in future CEAs. Data from the PAS study [32] were used to re-analyze a CEA with addition of partial behavioral change estimates based on six months smoking status and self-efficacy measures. Results of this model-based, simulated approach were compared to observed, trial-based results of Smit et al. [34]. Findings showed comparable results: the most intensive intervention (MTC) showed higher costs and lower effects compared to both the less intensive intervention (MT) and CAU in both the observed and simulated CEA. MT showed higher costs compared to CAU, however, effects were also somewhat better. Handling a WTP of €18,000 [34,42], MT is the most cost-effective intervention for both the trial- and model-based approach. Based on these findings, it could be concluded that modeling cognitive parameters in CEA can give a valid estimate of future cost-effectiveness at 12 months, based on six months costs, effects and cognitions. However, in the simulated CEA, uncertainty regarding data inputs was high. The probability of MT being cost-effective was 88% with a WTP threshold of €18,000 in the observed, trial-based CEA versus 53% in the present study.

Modeling future behavior change may be advisable for two main reasons. First, many intervention studies have a relatively short follow-up period of six months or less. Delayed behavior change can occur after a study period ends, which may lead to biased (cost) effectiveness results [3,9,43,44]. When people attempt to change habitual behaviors, the likelihood of relapsing to their old habit after a while is high. Certainly in smoking cessation research, where the majority of attempts will fail, this is widely acknowledged [45,46]. The issue here, therefore, is not whether delayed behavior change will occur after a follow-up of less than 12 months, but rather to what degree this occurs and more specifically, whether this occurs differentially depending on a particular intervention. For example, the present study showed that the observed CEA at six months (with a WTP of €18,000, CAU was most cost-effective) differed from the observed 12 months cost-effectiveness (using the same threshold for the WTP, MT was most cost-effective). Also, Oldenburg et al. [47] showed varying cost-effectiveness results comparing short-term (<six months) with long-term behavior change (>six months). Apparently, the MT either more effectively prevents relapse in the second half of the year following the quit attempt, or increases the chance of a renewed quit attempt. For the purpose of accounting for delayed behavior change, simulated CEA may be useful for examining the cost-effectiveness of an intervention over longer time-periods of months or even years.

Second, modeling of future behavior change by means of cognitive parameters provides a way to deal with missing behavioral endpoints for CEA research. For example, CEAs of interventions aimed at prevention in health promotion are scarce [e.g. 48,49,50] mostly due to missing endpoints of the intended behavior. Often, the aim of these interventions is to change cognitions associated with the behavior to be altered. As changes in cognitions are assumed to lead to changes in behavior, modeling these parameters can contribute to an approximation of future (cost-)effectiveness. Also, effectiveness data from existing trials that were not originally developed with the aim of a CEA are often unsuitable for CEAs due to a lack of adequate behavioral endpoints. Potentially, substituting behavioral endpoints by cognitive measures, which are often available, can make many more health promotion programs available for health economists to evaluate on their cost-effectiveness.

Obviously, the predictive value of the cognitive parameters should be high and empirically supported as this is prerequisite for valid (cost-)effectiveness prediction. Which specific cognitive parameters should be chosen might depend on the behavior to be predicted. Moreover, time variations should be taken into account as well. In the present study, Cox regression analyses with time-varying covariates were applied to examine the association of cognitions and smoking status at multiple measurements over time. Several studies found changes in cognitions to be relevant for the prediction of future behavior change [e.g. 29-31,51]. Therefore, solely focusing on a single point in time to predict future behavior may ignore important timing information and may consequently lead to biased predictions. The present study showed an univariately explained variance of approximately 25% of time-varying self-efficacy to smoking cessation. In addition, tests of the proportional hazard assumption implied that the hazard ratio could be assumed to be constant over time. In combination with information regarding smoking status, changes in self-efficacy from six weeks to six months could therefore be extrapolated to the prediction of 12 months smoking behavior.

Some limitations have to be noted. First, the reliability of the social modeling construct was not sufficient, but did appear to contribute significantly to the time-varying model of smoking cessation. This effect may therefore be a result of measurement error. However, this parameter was not included in the predictive model and could therefore not have affected these results. Second, some states that were distinguished in the predictive model were empty, and consequently assumptions regarding the probabilities had to be made. Potentially, larger datasets could have estimated these probabilities more accurately. However, it remains questionable if this would have affected our results. Lastly, not all significant cognitive parameters of smoking cessation found in the multivariate Cox regression model were included in the predictive model, as this would reduce parsimoniously and applicability of the presented method.

Many decision analytic models exist in health economic research. As models are a simplification of reality, uncertainty will always be present. Uncertainty is pervasive in CEAs and exists because we can never perfectly predict what the mean costs and outcomes associated with the use of a particular treatment will be [52]. Moreover, reliance on solely intermediate outcomes may both over- and underestimate final outcomes [1]. Nonetheless, the present study showed promising results for dealing with problems as delayed behavior change and missing endpoints by including partial behavior change in CEA. More information on additional cognitions and demographics in the model would probably imply less uncertainty, but also comes with more complexity and data requirements.

Handling a WTP of €18,000, the model-based 12 months CEA showed results largely similar to that of the observed CEA, in spite of the models' uncertainty. Our predictive CEA model was therefore validated by the true data. The present study showed promising results for dealing with problems as delayed behavior change and missing endpoints by including partial behavior change in CEA. Using a cognitive parameter to enhance the estimation of the true behavioral outcome seems a feasible, but also valid way to estimate future cost-effectiveness outcomes. As this is the first validation study of this kind in the field, the present study contributes uniquely to research in this domain.

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8

General discussion

General discussion

CEAs are considered an increasingly important tool in health promotion and psychology. In health promotion adequate effectiveness data of innovative interventions are often lacking [1]. In case of many promising interventions the available data are inadequate for CEAs due to a variable follow-up length or a lack of validated behavioral endpoints. Yet, in many of these cases effects on cognitive variables, such as intention and self-efficacy, are available. Modeling of cognitive parameters provide a way to overcome variations between studies, by estimating the required behavioral endpoints for use in CEAs.

The research described in this thesis was initiated to develop a method to include partial behavior change in CEA by modeling cognitive parameters of behavior change. It aimed to accomplish two goals. First, to provide a method that can give more insight in long term effectiveness of behavioral interventions, because it provides a way to look beyond measured (intermediate) endpoints in available data (by predicting them). And second, to develop a method that can contribute to the standardization of CEAs of behavioral interventions, as it will provide the technology to model from varying (cognitive or behavioral) endpoints to a single estimated endpoint of behavior change.

Relevance

In the systematic review (*chapter 2*) it was found that until recently, few studies have accounted for cognitive intermediate changes in current CEAs of behavioral interventions [2]. The potential value of doing so, however, is to some extent recognized. Two different frameworks were distinguished for including cognitive measures in CEA. In the first framework, cost-effectiveness results were calculated for changes in cognitions as secondary outcome measures, besides the cost-effectiveness for the primary, final endpoint. In the second framework, which was applied in the subsequent chapters, cognitive parameters were modeled to predict future cost-effectiveness at the final endpoint (i.e. behavior). Both approaches assume that behavioral interventions aim to accomplish behavior change through changes in cognitions. Consequently, changed cognitions are assumed to increase the chance of behavior change after the final follow-up. However, the second framework takes the application of cognitions one step further, by actually modeling these cognitive parameters to the final endpoint of behavior. This method expands the range of outcomes measures that are suitable for CEA research.

As modeling of future effects is already common in the field of health promotion it is rather remarkable that modeling of cognitive parameters to future behavior is not fully recognized yet. Multiple models exist that extrapolate observed smoking-related behavior to estimates of incidence, prevalence, mortality, progression and healthcare costs of several diseases [e.g. 3-8]. Variations due to length of follow-up and outcomes measured are captured in these models, and decisions based on future results can be made. For example, Hoogendoorn et al. [9] estimated the long-term cost-effectiveness of multiple smoking cessation interventions among COPD patients by means of a COPD disease progression model. Both behavioral and pharmaceutical interventions were assessed, based on their quit rates at the end of the follow-up periods. However, behavioral interventions aim to accomplish behavior change by means of changes in cognitions. Partial behavior change could have been present at the behavioral intermediate endpoint used, and thus may imply biased effect rates of the interventions under study. Consequently, CEA results may have over- or underestimated the relative cost-effectiveness of these interventions.

To examine the hypotheses stated above, in *chapter 3* and *4*, the cost-effectiveness of the SMOKE study was examined [10]. In this study, two smoking cessation interventions were compared for their (cost-)effectiveness among COPD outpatients [11]. Re-analyses of the CEA with inclusion of partial behavior change by modeling the stages-of-change showed deviating results [12]. Although the observed, trial-based CEA already showed the most intensive intervention to be dominant, compared to a medium intensive intervention, dominance was more obviously present when future quit effects were modeled based on literature's probabilities for smoking cessation one year later. Naturally, as relapse is also likely to occur among those who had already quit, this was also accounted for. Unfortunately, validation of this methodology within the dataset was not possible due to data constraints. Nonetheless, results visualized the bias that may be present in interpreting current cost-effectiveness results for interventions that aim to change behavior through changes in cognitions. For smoking cessation, pharmaceutical interventions are generally found cost-effective compared to behavioral interventions [e.g. 9,13]. The results found in this thesis suggests that such findings might need some reconsideration and partial behavior change has to be considered. We probably should look beyond limited follow-up periods for these intervention, by means of modeling cognitive parameters of behavior change.

Validity intermediate outcomes

Of course, the validity of intermediate outcomes in CEAs depends on the strength of the evidence that links the intermediate to the final health outcome of interest. A causal relationship between intermediate behavior change (cognitive parameters) and the final endpoint (behavior change) is a precondition to be able to predict future behavior. In *chapters 2* and *4* cognitive parameters were assumed valid if these were derived from empirically well-tested theories. A strong theoretical model can help to justify the choice for cognitive intermediate outcomes. In this dissertation we mainly built the models based on the Transtheoretical Model (TTM) [14], the Theory of Planned Behavior (TPB) [15,16], the Social Cognitive Theory (SCT) [17] and the ASE Model [18], currently known as the I-Change model [19]. The predictive validity of the TTM, however, has been discussed in literature. Critiques mainly concern its supposed usefulness in stage-based, tailored interventions with superior effectiveness [20-23]. The stages-of-change construct itself, though, has received strong empirical support in multiple areas of health promotion [20, 24,25]. Although it cannot simply be assumed that progression in stages-of-change automatically leads to behavior change on the individual's level [20,26], at group level it is more likely to reach the intended behavior when the stage-of-change is more proximal to behavior change. To deal with this particular issue, transition probabilities for the pre-action stages were calculated. These probabilities reflected the chance to reach behavior change at some future end point, based on the current stage participants were in. Unfortunately, transition probabilities were not available in literature for this specific population and time horizon and a weighted average of several transition probabilities among different subgroups and time horizons had to be used in the study reported in *chapter 4* [12]. Also, for generalization of this methodology to other life style behaviors, this may be a limitation. TTM was originally designed to describe addictive behaviors and was based on research of self-initiated quit attempts by smokers [27]. It has been largely studied in the area of smoking cessation, and has increasingly gained attention for other behaviors, such as dietary changes and screening behavior [28]. Despite the growing amount of studies on these behaviors, transition probabilities may not be yet that readily available. Moreover, applying stages-of-change to complex health behaviors such as physical activity and diet may be more difficult. Physical activity, for example, is not a single behavior but a complex set of different specific actions [20].

Economic evaluations require data for the assessment of the cost-effectiveness and its prediction models of healthcare treatment and programs. The gold standard approach is to conduct a systematic review of the relevant clinical literature [29]. However, for the present studies and intermediate outcomes this data may not be available in literature for different subgroups or behaviors under study. In our view, the optimal approach to indicate valid cognitive intermediate outcomes of the intended behavior in the target population, would be to analyze the predictability of the cognitive parameters in the data itself. In *chapter 6* it was underlined that even between two similar RCT's of smoking cessation among cardiac patient, the predictive value of the time-varying multivariate models was highly variable (16.3% versus 35.7%). Thus, transition probabilities will depend on specific characteristics of population, study design and measures, target behavior, and intervention. *Chapters 5* and *6* presented a method to analyze relevant cognitions in the data itself to capture the time-varying covariates of behavior change. Congruent with literature [e.g. 30-35], self-efficacy and intention to quit showed to be valid predictors of smoking cessation, both in a COPD and cardiac patient population. Moreover, *chapter 5* showed that from a time-varying approach other cognitive parameters may emerge than from a static regression analysis using single points in time to predict future behavior. At least three time assessments are needed for applying such analyses to reflect a minimal amount of time variation in cognitions and behavior. A first strength of this dynamic method is that it captures both variations in cognitions and smoking behavior. Besides the ability to include time-varying cognitions, it can also be accounted for the fact that people may relapse several times from initial behavior change, before they finally accomplish behavior change. For example for smoking cessation, a person may quit and relapse several times before he or she reaches abstinence. Accounting for time-varying behavior enhances the amount and validity of information put in the model and hence its ability of reflecting true covariates of smoking cessation.

A second strength lies in the ability to not just capture predictors of behavior change, but influences of past behavior may additionally be reflected in these cognitive predictors. Moreover, the cognitive parameters are indicators of behavior change, instead of pure predictors. The cognitive parameters were measured simultaneously with smoking cessation at the follow-ups and mean values between two successive measurements of each parameter were calculated to examine its association with smoking cessation at the last of these two measurements. This means that the time-varying parameters are partly based on a value that coincides with the assessment of smoking cessation. Moreover, a person may have quit smoking shortly before the assessment, but also for several months. Therefore, it can be presumed that the parameters partly reflect an effect of prior behavior. *Chapter 5* showed the importance of including this relation in a time-varying regression model. The explained variance of the model using the cognitive value assessed at the previous measurement to predict behavior at the next, results in far less explained variance (20.5%) compared to the model using mean values between time assessments to predict the latter of these two measurements (37.2%). This last model accounts for a reciprocal relation of cognitions and behavior. This reciprocal relation is in line with for example the SCT [17,36], but also the TPB [37]. These theories state that people are actors as well as products of their environments. Other studies have underlined the strong association of, for example, abstinence self-efficacy with smoking cessation [e.g. 32]. Ignoring this reciprocity between cognitions and behavioral experiences thus implies ignoring important variance. The most important cognitive parameters of behavior change are characterized by both a strong predictive value, as a strong responsiveness to prior behavior change (or maintenance). And that is exactly intended to be underpinned with time-varying analyses. By recognizing the reciprocal relation, interventions can anticipate on these 'learning' effects by intervening in case of an in- or decrease in response to behavior change (both quit and (re)lapse). In *chapter 6*, for example, time-varying analyses by means of Cox regression showed that hazard ratios were not constant across the time periods analyzed. In particular, a positive increase in mean scores of intention to quit and self-efficacy predictive for smoking cessation was only observed round the end of the intervention period. This finding suggests that the effort to reinforce abstinence self-efficacy does not stop after intervention delivery, but should preferably be continued, at least for these patients groups.

Remarkable from a theoretical perspective [16,37] was that findings from both samples showed a lack of association between attitudes and smoking behavior in a time-varying analysis for both COPD and cardiac patients. A reciprocal relation between attitude and previous behavior could explain this, as someone may have adjusted its attitude towards smoking. For example, outcomes may be disappointing for these patients groups due to lacking immediate perceived physical improvements. Also, for both disease groups there is a strong need to quit smoking. For cardiac patients, the prognosis improves considerably after smoking cessation [38]. Furthermore, smoking is the single most important way for affecting outcomes in all stages of COPD [39]. Thus, as the need to quit smoking remains strong, it is likely that the attitude towards quitting remains relatively stable over time, as shown by the analyses in *chapters 5* and *6*.

Stage-based versus continuous variables

Both constructs of stage-based theories, such as TTM, and construct of dimensional theories of behavior change, such as TPB [16,40] and the ASE model [18], showed to be feasible to incorporate in CEA. However, stages-of-change are qualitatively discrete stages and the dimensional theories provide a multidimensional continuum in which separate stages are not distinguished. In *chapter 7* this latter issue was dealt with, by first examining which cognitive factors are the most important predictors of behavior, and second by dividing these cognitions into categories. For this purpose a combination was constructed between level of smoking status and level of self-efficacy. This approach may seem contradicting the multidimensional continuum as proposed by the relevant theories, as a 5-point Likert scale was used to measure a continuous variable. However, there appears to be consensus in methodological literature that analyses based on (ordinal) 5-point scales in general produce findings similar to data obtained with interval scales [41-43].

Time horizon

The time periods that were used for estimating transition probabilities may be crucial for the validity of the final endpoint to be predicted. For example, *chapter 5* showed time-varying effects of self-efficacy on smoking cessation. However, when more closely examining both analyzed time periods, it was shown that its influence was strongest in the period from six to 12 months. Similarly, in *chapter 6*, for both samples the initial hazard ratios of respectively intention to quit and self-efficacy were negative at baseline, becoming positive round the first follow-up, and then increased over time. This means that particular attention should be given to the time period used for estimating transition probabilities. The baseline values of cognitive parameters predominantly reflect pre-quit levels. The important reciprocal relation, as suggested before, is most likely to occur after intervention delivery. This period would probably give the best reflection of the most important indicators of behavior change and may therefore provide the valid time period to calculate transition probabilities for methods described in *chapter 7*.

Complexity versus simplicity

The aim of the present dissertation was to provide a feasible and valid approach to include partial behavior change in CEAs of behavioral intervention by modeling its cognitive parameters. For both *chapters 4* and *7*, one single cognition was applied for the prediction of future behavior change. Consequently, as was shown by the cost-effectiveness planes and cost effectiveness acceptability curves, uncertainty around data inputs for the models did occur. Potentially uncertainty can be reduced by incorporating more cognitions and other predictive variables. For example, the Cox regression analysis in *chapter 7* not only found time-varying self-efficacy to be significantly related to smoking cessation. Also, time-varying intention to quit, having experienced a previous quit attempt at baseline and time-varying social modeling added an extra explained variance of approximately 3%. However, incorporating these variables to our model would increase the complexity considerably. Moreover, the sample size of the study, as it is in similar studies, constrained the expansion of the model in terms of extra variables. Thus, in this case more would be less and reduce the model's parsimoniousness. However, is the presented method worth the increased uncertainty? Health economic evaluations in general are vulnerable to manipulation due to the use of primary data and the arbitrary definition of outcomes. The use of a meaningful intermediate outcome is a precondition for the validity of the study. Predicting full behavioral change after the intervention period ends, and thus substituting a missing future endpoint will almost inevitably increase uncertainty compared to using an observed final endpoint. However, uncertainty is pervasive in CEA and exists because we can never predict for certain what the mean cost and outcomes associated with a particular treatment will be [44]. The question here is not if uncertainty is acceptable in models such as these, but rather what degree of uncertainty will be tolerable. The purpose of models is not to predict the results of even an ideal pragmatic trial (or observational study) but to inform decision making at a particular point in time. Therefore, the testable and falsifiable hypothesis by modeling is that an optimal informed decision will be made at time t by using a model compared to not using it [45]. This could for example be seen in *chapter 7*. Different decisions would have been made if only information had been available at six months follow-up, compared to (both observed and simulated) results at 12 months follow-up.

Missing values in health promotion research

In health promotion, as in other areas, missing values are common. Often an 'intention-to-treat' procedure is applied, treating patients lost to follow-up as failures. However, the analyses presented in this thesis not only face missing values in measured behavioral endpoints, but also in values of cognitive parameters. As the methods presented estimate transition probabilities based on the study's real data, instead of reviews or meta-analyses, this has consequences for model developments. Therefore, in *chapter 7*, a separate category was incorporated for those participants who reported missing values. For behavior change, the intention-to-treat procedure was retained. Ignoring or imputing missing values was therefore superfluous, and could add value to the estimated model. This makes the method robust and insensitive for missing data, and is therefore regarded as a strength of the predictive model.

Strengths and limitations

In this thesis a method was developed to account for missing endpoints and delayed behavior change in health promotion research. The described approach can be applied to several health behaviors and interventions, as cognitions within a study's own dataset are analyzed of which transition probabilities can be obtained to predict future behavioral endpoints. Also, the time-varying analysis employed for this purpose is not restricted to static endpoints to be predicted by cognitions measured at one point in time. It considers fluctuations in both behavior and cognitions to reflect the true covariates of the behavior change process, thus acknowledging the reciprocal nature of the cognition-behavior association. This makes a more valid prediction of future behavior possible. Furthermore, by being able to describe time variations even when just two time periods are considered, the practical applicability to existing RCTs is high. Moreover, the large amount of missing values that is common in RCTs in health promotion can be accounted for, as was shown in the presented models in *chapters 4* and *7*. Finally, this thesis presents the first unique study in which actual predictions of future cost-effectiveness by modeling cognitive parameters is validated with true, observed CEA results. The method presented is relatively simple and easily applicable to other datasets. In summary, both feasibility and validity of the method can be confirmed by results of this thesis.

Some limitations need to be considered. First, this thesis has mainly considered cognitive parameters of the ASE model and the TTM. Other potential cognitive factors of behavior change were not considered or were not measured in the datasets used. Furthermore, distal factors of behavior change such as personality or demographics were not considered in CEA, although they are distinguished as predictors in the theoretical models described in this thesis. Both theories applied in this thesis, however, are built on an extensive body of theoretical and empirical work. Self-efficacy, for example, is a construct originally derived from Bandura's SCT [17], but adopted by most other theoretical models. The constructs that were considered in our studies do represent the currently dominating social cognitive variables.

Second, the focus of the thesis was not on the health effects in the long term, but rather on assessing and predicting the risk factor (i.e. behavior change) that causes or exacerbates disease. For decision makers, however, future health benefits and costs are more informative than the cost per quitter following the intervention. For those purposes, the presented model could serve as an extension of longer term predictive models.

Third, each population and behavior may have different cognitions and values that are valid to predict future behavior. Literature does not (yet) have transition probabilities available to generalize findings for larger groups beyond the trial. On the other hand, a strength of the presented method in this thesis is to obtain probabilities from the original trial data to reduce uncertainty.

Fourth, in all studies presented in this thesis, smoking abstinence was based on self-reported measures. As deceivers are common in smoking cessation research when compared to biochemically validated measures [46,47], the amount of people that had successfully quit smoking is likely to be overestimated.

Fifth, in *chapter 7* the Cox regression analyses examined multiple time periods, which indicated the important time-varying cognitive parameters of behavior. However, transition probabilities were estimated based on only one time period and did not account for time dependency. This was justifiable, as the test for the proportional hazard assumption showed that hazard ratios could assumed to be equal for the multivariate model. For cognitive parameters in studies where this assumption does not hold, calculating probabilities based on one single time period may potentially be a problem. In this case, the model should be expanded to account for time dependency.

And lastly, in this thesis our innovative procedure was validated only once (*chapter 7*), with a relative short time horizon of six months (predicting from six to 12 months), on a single health behavior. Obviously, this will need further replications and extensions.

Future directions

Several directions for future research can be given, based on this thesis. Further research should aim at replicating these analyses in other populations and other behaviors (and other predictors and varying time horizons). For example, in the area of mental health promotion, CEAs are often limited by short follow-up periods, as effectiveness is commonly based on comparison to wait list conditions [e.g. 48, 49]. Self-efficacy and intention in the present thesis showed to be the important predictors of smoking cessation among COPD, cardiac patients and the general population. However, for areas of, for example, mental health promotion other predictors might be influential which should therefore be examined before incorporating in CEA.

Also, for health promotion, other cognitions may be considered. Examples are constructs such as action planning [50] and implementation intentions [51], which have increasingly gained attention and are assumed to influence the relation between intentions and behavior [e.g. 17,19]. These constructs may be of particular importance for explaining longer term effects of behavior. Another growing domain of predictors of behavior change are implicit cognitions [52,53], which have shown to contribute uniquely, over and above explicit cognitions, to the prediction of, for example, drinking behavior [53]. The method presented in *chapters 5* and *6* can easily be applied for these purposes.

Second, the method presented could serve as an extension of several predictive models for disease progression in the literature [4-7] , in which mortality and death are predicted, based on, among other factors, smoking cessation. It would be interesting to explore long term effects on health outcomes of the incorporation of behavior change by means of modeling cognitive parameters. Behavioral intermediate outcomes that are currently used to estimate incidence and prevalence of mortality and death may be substituted or preceded by cognitive parameters to account for delayed behavior change or missing endpoints of behavior.

Third, behavior change is a complex process. More research is needed on the time variations in cognitions and behaviors in multiple areas to make inclusion for CEA possible. Also, more complex models may eventually be considered. The presented methods made predictions for groups, whereas particularly for cognitive and behavior change, for example, demographics and personality are important factors that are assumed to influence cognitions. Also time dependency in CEA modeling by means of cognitive intermediate outcomes was not yet explored, as the focus was on parsimoniously. Currently, strong predictors of behavior were specified by means of a time-varying approach. However, transition probabilities (*chapter 7*) were based on one time period, which may not be valid if time dependency is present for the cognitive parameters' hazard ratios for behavior change. Expansion of the model be therefore be considered in future research. Perhaps better and more valid estimates of behavior could be made by handling techniques as discrete event simulation (DES) or longer time Markov modeling [54,55]. However, this could only be possible if larger datasets exists to estimate the needed parameters.

Conclusions

This thesis presents a feasible and potentially valid method to deal with delayed behavior change and missing endpoints in CEAs of behavioral interventions. The method described consists of several steps. First, for considering relevant cognitions of behavior change, time-varying analyses have to be applied, which has shown to be suitable for commonly used intervention designs. Second, transition probabilities between cognitive intermediate states and behavior change should be obtained, preferably from the original data or from literature. Third, costs have to be extrapolated to a future time period, preferably based on the original data for the analyzed time period. Finally, a predictive model can be constructed based on the future costs and effects to estimate future cost-effectiveness results. Ultimately, modeling cognitive parameters to predict behavior change at some future endpoint may have important implications for health policy and health behavior research in particular.

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Samenvatting

(Dutch summary)

Samenvatting

Kosteneffectiviteitsanalyses (KEAs) worden steeds vaker toegepast voor evaluatie van gezondheidsbevorderende en psychologische interventies. Echter, in het gebied van de gezondheidsbevordering wordt de effectiviteit van innovatieve interventies vaak in beperkte mate onderzocht. In het geval van meerdere veelbelovende interventies zijn de aanwezige databestanden niet bruikbaar voor KEAs vanwege variabele follow-up periodes van interventies of een gebrek aan gevalideerde uitkomsten. Maar vaak zijn wel effecten op cognitieve variabelen, zoals intentie en eigen effectiviteit, gemeten. Om een oplossing te bieden voor deze variaties tussen studies kunnen cognitieve parameters van gedrag gemodelleerd worden met als doel de vereiste eindpunten van gedrag te schatten voor toepassing in KEA.

Het onderzoek dat beschreven is in dit proefschrift betreft de ontwikkeling van een methode om gedeeltelijke gedragsverandering in KEA te includeren door het modeleren van cognitieve parameters van gedragsverandering. De volgende doelstellingen zijn onderzocht: ten eerste, het creëren van een methode dat inzicht kan geven in effectiviteit van gedragsinterventies op de langere termijn, door verder te kijken dan gemeten (tussentijdse of intermediaire) uitkomsten in beschikbare data. Een tweede doel was om een methode te ontwikkelen die kan bijdragen aan de standaardisatie van KEAs van gedragsinterventies. Beide doelstellingen zijn onderzocht door dezelfde methode toe te passen: voorspellen van eindpunten van gedrag door het modeleren van intermediaire uitkomsten van gedrag.

Hoofdstuk 2: Systematische review naar de rol van cognities in kosteneffectiviteitsanalyses van gedragsinterventies

Het eerste artikel in het proefschrift beschreef een systematische review van de literatuur met als doel te onderzoeken welke cognitieve uitkomsten van gedragsverandering kunnen worden geïdentificeerd in KEAs en te evalueren hoe deze uitkomsten geïncludeerd zijn in KEAs. Twaalf studies werden gevonden die voldeden aan de vooraf gestelde in- en exclusie criteria. Hieruit werd geconcludeerd dat tot op heden weinig KEA studies zijn gevonden die rekening houden met cognitieve intermediaire veranderingen die alsnog kunnen leiden tot het gewenste gedrag. De potentiële waarde van het includeren van cognitieve veranderingen was echter in zekere mate wel erkent in de literatuur. In de resultaten konden twee verschillende benaderingen van includeren van cognitieve intermediaire veranderingen worden onderscheiden. In de eerste benadering werden kosteneffectiviteitsuitkomsten berekend voor veranderingen in cognities als secundaire uitkomsten van KEA, naast de primaire uitkomst van het uiteindelijke gedrag, waardoor er dus meerdere uitkomsten van KEA werden berekend. In de tweede benadering werden de cognitieve intermediaire uitkomsten van gedrag gemodelleerd om een schatting van toekomstig gedrag te kunnen geven. Met behulp van deze voorspelde effectiviteitsmaat werd de kosteneffectiviteit berekend. In beide benaderingen wordt impliciet of expliciet de aanname gedaan dat gedragsverandering kan worden bereikt door veranderingen in cognities ten aanzien van het desbetreffende gedrag. Uit deze review kan geconcludeerd worden dat voor het uitvoeren van KEAs van gedragsverandering het includeren van gedeeltelijke gedragsverandering door middel van cognities overwogen zou kunnen worden voor het doen van uitspraken over zowel effectiviteit van interventies gericht op gedragsverandering, als kosteneffectiviteit.

Hoofdstuk 3: Kosteneffectiviteitsanalyse van de SMOKE studie

In hoofdstuk 3 werd een KEA uitgevoerd van de SMOKE studie. De kosteneffectiviteit van een hoog intensief stoppen-met-roken programma (SmokeStopTherapy; SST) is vergeleken met een matig intensief stoppen-met-roken programma (Minimal Intervention Strategy for Lung patients; LMIS) voor poliklinische COPD patiënten. De SMOKE studie is een gerandomiseerd onderzoek naar de effectiviteit van de SST versus de LMIS met een studieduur van 12 maanden. De primaire uitkomstmaat was de gevalideerde continue abstinentie. Voor de KEA werd het gezondheidszorg perspectief gehanteerd en uitkomsten werden bepaald in termen van gewonnen extra stoppers, voorkomen exacerbaties en voorkomen ziekenhuis dagen. Resultaten lieten zien dat een gemiddelde COPD patiënt die was toegewezen aan de SST €581 gezondheidszorgkosten genereerde versus €595 voor de patiënten toegewezen aan de LMIS. Ook was de SST geassocieerd met een lager gemiddeld aantal exacerbaties per patiënt (.38 versus .60), lager aantal ziekenhuisdagen (.39 versus 1), en een hoger aantal stoppers (20 versus 9) tegen lagere totale kosten. Hieruit blijkt dat de SST de LMIS domineert. De hoog intensieve SST bleek dus goedkoper en effectiever te zijn ten opzichte van de medium intensieve LMIS na één jaar follow-up.

Hoofdstuk 4: Modeleren van de ‘stages-of-change’ in de kosten-effectiviteitsanalyse van de SMOKE studie

Hoofdstuk 4 beschreef de her analyse van de KEA van de SMOKE studie zoals werd uitgevoerd in hoofdstuk 3. De aanleiding hiervoor was dat KEAs doorgaans een dichotome uitkomstmaat hanteren, zoals bijvoorbeeld succes of falen. Maar gedragsverandering is een complex proces waarin verschillende stappen worden genomen om tot een verandering in gedrag te komen. Hierdoor is het mogelijk dat vertraagde effecten van de interventies voorkomen nadat de studie periode geëindigd is. Deze worden echter niet meer meegenomen in de analyse. Dit kan leiden tot onder- of overschatting van deze interventies. Omdat de uitkomstmaat voor gedragsinterventies vaak gedichotomiseerd is, kan dat in sterkere mate verwacht worden. Door cognitieve, intermediaire uitkomsten van gedragsverandering te modeleren kan hier echter voor gecorrigeerd worden. In dit hoofdstuk is dit gedaan door het modeleren van de 'stages-of-change' van het TransTheoretische Model (TTM) van gedragsverandering. Deze 'stages-of-change' beschrijven de verschillende fases van intentie tot gedragsverandering. De indeling van de respondenten in deze fases werd verkregen uit de beschikbare data op het meetmoment op 12 maanden. Overgangskansen voor het modeleren van gedragsverandering op 24 maanden follow-up werden verkregen uit de literatuur. Resultaten lieten zien dat voor de eerste 12 maanden, de hoog intensieve interventie (SST) domineerde in 58% van de gesimuleerde gevallen. Na het modeleren van de cognitieve fases van gedragsverandering naar een toekomstige follow-up van 24 maanden, domineerde de SST in ongeveer 79% van de gevallen. Deze studie liet zien dat het modeleren van toekomstige gedragsverandering in deze KEA van een gedragsinterventie de resultaten van de originele KEA heeft bevestigd en zelfs versterkt. Dit impliceert dat in het geval van een KEA waar de resultaten rondom de grenswaarde liggen, het mogelijk is dat het modeleren van gedeeltelijke gedragsverandering leidt tot een andere beslissing omtrent een interventie. Uiteindelijk kan dit consequenties hebben voor de ontwikkeling van gezondheidszorgbeleid in het algemeen en meer specifiek voor de adoptie van gedragsinterventies.

Hoofdstuk 5: Een baseline versus tijd variërende analyse van cognitieve determinanten van stoppen met roken bij COPD patiënten

In hoofdstuk 5 werd gericht op de analyse van cognitieve determinanten van gedragsverandering voor gedragsinterventies. De focus lag ook hier op het proces van gedragsverandering, waarin over de tijd verschillende cognitieve stappen tot gedragsverandering worden genomen. Om gedrag te voorspellen richten de meeste onderzoekers zich op cognitieve determinanten van gedrag gemeten op een enkel punt in de tijd. Ook wordt door onderzoekers voor het voorspellen van gedrag gebruikt gemaakt van (meerdere) dagelijkse metingen, wat in de praktijk lastig toepasbaar in termen van uitvoerbaarheid en kosten. In dit hoofdstuk werden de psychologische determinanten op verschillende tijdspunten onderzocht die resulteren in stoppen met roken op doorgaans gebruikte follow-up perioden. Er werd hier rekening gehouden met twee aspecten: de in tijd variërende aard van het effect (bijvoorbeeld bij stoppen met roken) en de in tijd variërende aard van de determinanten. Ook hier was de data van de SMOKE studie gebruikt waarin twee stoppen-met-roken interventies werden vergeleken voor COPD patiënten. De determinanten eigen effectiviteit, sociale steun, attitude en de beschrijvende sociale norm werden gemeten op het startpunt van de interventie en op zes en 12 maanden follow-up. Er werden twee verschillende Cox regressie modellen geschat: 1) met tijd variërende determinanten die voorspellend zijn voor stoppen-met-roken op zes en 12 maanden en 2) met determinanten op een enkel tijdspunt die stoppen-met-roken voorspellen op een enkel eindpunt. Resultaten lieten zien dat in een tijd variërende analyse, eigen effectiviteit de belangrijkste voorspeller bleek te zijn. In tegenstelling hierop bleken attitude en de beschrijvende sociale norm de belangrijkste voorspellers in de statische analyse waarin determinanten op het startpunt meegenomen zijn. In dit artikel is het onderscheid tussen statische en tijd variërende analyses aangetoond, alsmede ook een reciproque relatie tussen eigen effectiviteit en stoppen met roken. Ook liet deze studie zien dat Cox regressie analyse een praktisch toepasbare en valide methode is om het tijd variërende aspect in gedragsverandering te onderzoeken.

Hoofdstuk 6: Vergelijking van tijd variërende cognities van stoppen met roken bij twee studies onder hartpatiënten

In hoofdstuk 6 werd de tijd variërende bijdrage van cognitieve determinanten van stoppen met roken onderzocht onder een andere groep patiënten. Cox regressie analyses werden toegepast op twee onafhankelijke, vergelijkbare datasets. In dit hoofdstuk werden secundaire analyses verricht op twee gerandomiseerde studies naar korte stoppen-met-roken interventies van gehospitaliseerde en poliklinische hartpatiënten. In beide datasets bleken de cognitieve determinanten eigen effectiviteit en de intentie om te stoppen sterke tijd variërende indicatoren van stoppen-met-roken te zijn over de volledige follow-up periode van één jaar, en voornamelijk in de periode nadat de interventie gegeven werd. Deze resultaten komen overeen met sociaal cognitieve theorieën van gedragsverandering. Een interessant gegeven in deze studie was dat beide cognitieve constructen een positieve invloed op gedragsverandering hadden nadat de interventie had plaatsgevonden. Dit hoofdstuk liet zien dat stoppen met roken een langdurig proces is waarin de interactie tussen eigen effectiviteit (en ook intentie om te stoppen) en stopgedrag het uiteindelijke succes van stoppen met roken op de lange termijn bepaalt. Ook uit dit hoofdstuk bleek dat tijd variërende analyses een valide en toegankelijke manier zijn om de onderliggende cognitieve trajecten van gedragsverandering te onderzoeken in datasets met een beperkt aantal tijdsintervallen.

Hoofdstuk 7: Modeleren van cognities in de kosteneffectiviteitsanalyse van de PAS studie

In het laatste artikel in dit proefschrift werd de methode die is toegepast in hoofdstuk 4 herhaald, maar nu ook gevalideerd aan de hand van geobserveerde data. Een KEA van een bestaande dataset van een driearmige gerandomiseerde online stoppen-met-roken studie (PAS studie) met een follow-up van 12 maanden werd hiervoor gerepliceerd. In dit hoofdstuk werd eerst bepaald wat de belangrijkste cognitieve voorspeller van gedrag is door middel van de Cox regressie analyses zoals gepresenteerd in hoofdstukken 5 en 6. Hieruit bleek dat eigen effectiviteit ook in deze dataset de sterkste voorspeller was voor stoppen met roken. Vervolgens werden de KEA resultaten na zes maanden follow-up berekend. In de derde stap werden de overgangskansen voor het modeleren van de cognitie eigen effectiviteit berekend. Dit werd gedaan door te berekenen wat de kans is dat iemand rookt of is gestopt op zes maanden follow-up, gegeven een combinatie van niveau van eigen effectiviteit en rookgedrag op zes weken. In de vierde stap werden deze overgangskansen geëxtrapoleerd naar de periode van zes tot 12 maanden follow-up en gebruikt om gedrag en kosteneffectiviteit te voorspellen op 12 maanden. In de laatste stap werden deze gesimuleerde resultaten vergeleken met de originele KEA resultaten om de validiteit van de gebruikte methode vast te stellen. Hieruit bleek dat de gesimuleerde resultaten grotendeels overeenkwamen met de originele, geobserveerde uitkomsten van CEA. In beide gevallen was de MT interventie (multiple tailoring) kosteneffectief vergeleken met de standaard zorg. MTC (multiple tailoring en counseling) werd in beide gevallen gedomineerd door de MT en standaard zorg. De gesimuleerde KEA kon worden gevalideerd door de werkelijke data. Het modeleren van cognitieve intermediaire uitkomsten zoals eigen effectiviteit om de toekomstige uitkomst van gedrag te schatten lijkt een toegankelijke en valide manier zijn om een benadering te geven van toekomstige kosteneffectiviteit van een interventie.

Hoofdstuk 8: Algemene discussie

In de algemene discussie van het proefschrift werden de resultaten van de voorgaande hoofstukken samengevat en bediscussieerd. Dit proefschrift liet zien dat het schatten van toekomstige kosteneffectiviteit mogelijk is door het modeleren van cognitieve intermediaire uitkomsten van gedragsverandering. De gepresenteerde methode biedt een oplossing voor ten minste twee moeilijkheden met KEAs van gedragsinterventies. Ten eerste kan vertraagde gedragsverandering dat niet wordt waargenomen tijdens een studieperiode worden gemodelleerd. Gedragsstudies hebben sterker last van onderschatting door beperkingen in follow-up duur. Hierdoor zouden gedragsinterventies in vergelijking met medische en farmacologische studies onder gewaardeerd kunnen worden. Een voorspellende kosteneffectiviteitsanalyse zou dat kunnen ondervangen. Een tweede aspect dat beperkingen heeft opgeleverd in de huidige traditie van KEA is dat van missende waarden van eindpunten van gedrag. Voornamelijk voor preventieve interventies geldt dat het te beïnvloeden gedrag pas lang na de studieperiode optreedt (of juist niet). Maar ook andere gezondheidsbevorderende interventies kunnen door praktische of financiële problemen eindpunten van gedrag niet altijd adequaat meten. Om gedragsinterventies onderling beter te kunnen vergelijken, wat betreft kosteneffectiviteit, is het nodig om de variatie in follow-up duur en kwaliteit van uitkomstmaten te reduceren. Het modeleren van cognitieve intermediaire uitkomsten kan ook hierin een oplossing bieden.

In dit hoofdstuk werden verschillende aspecten besproken waar rekening mee moet worden gehouden: de validiteit van de intermediaire uitkomsten, het gebruik van gefaseerde of continue cognitieve determinanten van gedrag, de tijdsperiode die gehanteerd moet worden, het hanteren van een complex versus een simpel model en het omgaan met missende waarden (in data) voor het schatten van toekomstig gedrag.

Aanbevelingen voor toekomstig onderzoek kunnen worden gedaan, zoals het verkennen van de mogelijkheden van de toepassing van de beschreven methodologie op andere onderzoeksgebieden van gedragsverandering zoals leefstijl of geestelijke gezondheidsbevordering. Tevens kunnen andere cognities bijdragen aan een betere benadering van voorspellen van gedrag en daarom worden overwogen. Verder kan de gepresenteerde methode mogelijk dienen als een uitbreiding van ziekte progressie modellen en zou de meerwaarde van een meer complex model nader onderzocht moeten worden.

Resumerend bestaat de gepresenteerde methode uit een aantal stappen. Ten eerste moeten tijd variërende analyses worden toegepast voor het analyseren van de relevante cognities van gedrag. Ten tweede moeten overgangskansen verkregen worden, bij voorkeur gebaseerd op de eigen data. Ten derde moeten kosten geëxtrapoleerd worden naar een toekomstige tijdsperiode, bij voorkeur gebaseerd op de eigen data. Ten slotte kan het voorspellende model dan geconstrueerd worden gebaseerd op de toekomstige kosten en effecten om toekomstige kosteneffectiviteit resultaten te schatten. Uiteindelijk zou het modeleren van cognitieve intermediaire uitkomsten naar toekomstig gedrag belangrijke implicaties kunnen hebben voor het gezondheidsbeleid in het algemeen en specifiek voor onderzoek naar gezondheidsgedrag.

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Rilana Prenger
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Curriculum Vitae

Curriculum Vitae

Rilana Prenger was born in Hardenberg on April 18, 1983. She graduated from secondary school (Atheneum) in 2002 at the Deltion college in Zwolle. From 2002 to 2007 she studied Psychology at University of Twente, where she graduated within the specialization Safety and Health. Her master thesis was about reduced smoking among 14–16 years old adolescents in lower secondary professional education. Rilana started her PhD project in September 2007 at the Faculty of Behavioral Sciences, department of Psychology, Health & Technology on assessing outcomes and cost-effectiveness of behavioral health interventions. During this project, Rilana participated in the PhD training program of the Interuniversity Research Institute for Psychology & Health and took multiple courses on Health Technology Assessment. The results of her PhD project are described in this dissertation.

Rilana Prenger is geboren op 18 april 1983 te Hardenberg. In 2002 heeft ze haar VWO diploma behaald aan het Deltion College te Zwolle. Van 2002 tot 2007 heeft ze Psychologie gestudeerd aan de Universiteit Twente, waar ze afgestudeerd is binnen de specialisatie Veiligheid en Gezondheid. Het onderzoek beschreven in haar masterthese was gericht op minderen met roken onder 14–16 jarige VMBO scholieren. In september 2007 is ze aan haar promotieonderzoek begonnen binnen de afdeling Psychologie, Gezondheid en Technologie van de Faculteit Gedragswetenschappen over het meten van uitkomsten en kosteneffectiviteit van gezondheid bevorderende gedragsinterventies. Tijdens haar project volgde ze het trainingsprogramma van de onderzoeksschool 'Psychology & Health', waarnaast ze diverse cursussen gericht op economische evaluaties heeft gevolgd. De resultaten van haar promotieproject zijn beschreven in dit proefschrift.

List of publications

Prenger R, Pieterse ME, Braakman-Jansen LMA *et al*. Dealing with delayed behavioral effects in health promotion by modeling cognitive intermediate outcomes in cost-effectiveness analyses: a validation study *Submitted*.

Prenger R, Pieterse ME, Braakman-Jansen LMA *et al*. A comparison of time-varying covariates in two smoking cessation interventions for cardiac patients *Submitted*.

Prenger R, Pieterse ME, Braakman-Jansen LMA *et al*. Cognitive covariates of smoking cessation: Time-varying versus baseline analysis *Submitted*.

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